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Clinical Trial Protocol: 15VR8

	Date
Version 2:	30 June 2016
Version 1:	19 November 2015

Study Title: An Open-Label, Long-Term Extension Study of the Safety of Somavaratan (VRS-317) in Adults with Growth Hormone Deficiency (GHD)

Study Number: 15VR8

Study Phase: Open Label Extension

Product Name: Somavaratan (VRS-317)

IND Number: 108471

Indication: Adult Growth Hormone Deficiency

Investigators: Multicenter

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SYNOPSIS: PROTOCOL 15VR8

SPONSOR
Versartis, Inc.

NAME OF FINISHED PRODUCT
Somavaratan (VRS-317)

NAME OF ACTIVE INGREDIENT
Somavaratan (VRS-317)

STUDY TITLE
An Open-Label, Long-Term Extension Study of the Safety of Somavaratan (VRS-317) in Adults with Growth Hormone Deficiency (GHD)

STUDY NUMBER
15VR8

PHASE OF DEVELOPMENT
Long-Term Extension Study

OBJECTIVE(S)

The primary objective of this study is:

- To evaluate the safety of somavaratan during long-term treatment in adults with GHD

The secondary objectives of this study are:

- To evaluate the dose (starting and maintenance) and the dose titration plan of twice-monthly somavaratan during long-term treatment
- To evaluate the immunogenicity of somavaratan during long-term treatment in adults with GHD by detection of anti-somavaratan antibodies (anti-drug antibodies, ADAs)
- To evaluate pharmacodynamic responses (IGF-I, IGFBP-3) during long-term somavaratan treatment

STUDY DESIGN

General
This open-label extension study will evaluate the safety of long-term twice-monthly administration of somavaratan in adults with GHD. This is an open-label, multicenter study open to subjects completing a Versartis adult GHD study as well as approximately 40 new somavaratan naïve subjects (either rhGH treatment naïve or currently receiving daily rhGH therapy). All subjects will receive twice-monthly (every 15 days ± 2 days) subcutaneous (SC) somavaratan. Doses will be titrated to each subject's individual IGF-I responses based on the IGF-I level 7 days post-dose until a maintenance dose is achieved. Maintenance dose is defined as an IGF-I value between 0 and 2.0 SDS for two consecutive 7 day post-dose time points (Day 8, peak level). Subjects receiving somavaratan once-monthly in this study (Protocol 15VR8) or in a previous somavaratan study (Protocol 15VR7), will have their dose decreased by half (minimum dose of 20 mg, 40 mg for women on estrogen, rounded down to the nearest even number) and will be titrated per the Dose Titration Plan (Table 2). New subjects enrolling in this study will be assigned to one of two cohorts and will receive a starting dose of 20 mg twice-monthly (40 mg for women on estrogen) (Table 1) and will be

titrated per the Dose Titration Plan (Table 2). Maintenance doses may be adjusted further based on PD data at the discretion of the Investigator or Medical Monitor.

Table 1 Study Drug Starting Dose Information:

Subject Cohort Assignment	Fixed Starting Study Dose	Frequency of Administration
Cohort 1: Adults with GHD irrespective of age and gender	20 mg	Twice-Monthly
Cohort 2: Women receiving oral estrogens	40 mg	Twice-Monthly

Table 2 Dose Titration Plan

Downward Dose Titration		
IGF-I at Day 8	**Cohort 1**	**Cohort 2**
0 to 2.0 SDS	No change in dosing	No change in dosing
2.01 to 3.0 SDS	4 mg dose decrement	4 mg dose decrement
Greater than 3.0 SDS	10 mg dose decrement	10 mg dose decrement
Upward Dose Titration[1]		
IGF-I at Day 8	**Cohort 1**	**Cohort 2**
-1.0 to 0 SDS	4 mg dose increment	10 mg dose increment
Less than -1.0 to -2.0 SDS	10 mg dose increment	20 mg dose increment
Less than -2.0 SDS	20 mg dose increment	40 mg dose increment

1: Maximum allowable dose is 250.0 mg

Study in clinic visits/blood sample collections will occur every week for the first 4 weeks of the study, followed by monthly in clinic visits until the subject has reached maintenance dosing. Some of the blood sample collections may be obtained in the subject's home throughout the study. Somavaratan doses will be administered in clinic During Month 1 and at each monthly Day 1 visit until maintenance dosing is achieved. After Month 1, Day 16 doses may be administered at home. In clinic visits will occur quarterly during the first year. Although quarterly visits will continue throughout the study, after the first year blood samples will be collected every 6 months, with intervening visits used for brief physical exams and collection of AEs and concomitant medications.

A total of up to 250 subjects will be enrolled.

Safety

Subjects will be monitored for safety throughout their participation in the study. Safety will be monitored by physical examination, inspection of injection sites, vital signs, ECGs (new subjects only), and clinical laboratory determinations. Adverse events (AEs) and concomitant medications (CMs) will be captured. AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE). AEs will be coded using the MedDRA dictionary and CMs using the WHO Drug Dictionary (WHODDE, WHO Drug Dictionary Enhanced).

For new subjects, electrocardiograms (12-lead ECGs, triplicate tracings) will be conducted at Screening and repeated at Day 1 and Month 4 at 3 days (±1 day) after dosing.

An external data safety and monitoring board (DSMB) will monitor and protect the safety of the study subjects throughout the study duration. DSMB meetings will occur twice yearly (approximately every 6 months).

The Stopping Criteria for individual subjects include:

1. The Principal Investigator (PI) and/or Medical Monitor conclude it is unsafe or not in the subject's best interest to continue.
2. IGF-I SDS ≥ 3.0 SDS on two consecutive Day 8 time points despite dose adjustments.
3. IGF-I SDS ≥ 2.0 SDS on two consecutive Day 8 time points despite dose adjustments and accompanied by clinically meaningful drug-related AEs, as determined by the Investigator and the Medical Monitor.

Subjects meeting individual stopping criteria will be withdrawn from the study.

The Stopping Criteria for the study itself include the determination that the study is unsafe to continue.

Pharmacokinetics (PK) and Pharmacodynamics (PD)

The PK parameter is somavaratan concentration and the PD parameters are serum IGF-I and IGFBP-3. All subjects will have blood samples collected for PK/PD assessments at Day 1 (pre-dose) and Days 8, 16, and 23 during Month 1 and at Day 1 (pre-dose) and at Day 8 monthly until dose stabilization is achieved. Once maintenance dosing is achieved, PK/PD samples will be collected quarterly at Day 1 and Day 8 in the first year and then every 6 months thereafter.

Immunogenicity

Immunogenicity will be assessed by measuring anti-somavaratan antibodies (anti-drug antibodies, ADAs) at baseline and every three months during the first year of this study and then every 6 months thereafter. Testing will follow a tiered approach consisting of screening, confirmation, titration and additional characterization of confirmed positive ADA samples.

Study Population

The study population will consist of adults age 18-75 who have well-established growth hormone deficiency (GHD). Eligible subjects will have completed a Versartis adult GHD study or will be included as new subjects who are either rhGH treatment naïve or transitioned from daily rhGH therapy to twice-monthly somavaratan. New subjects transitioning from daily rhGH therapy must discontinue daily rhGH use for a minimum of 14 days prior to somavaratan dosing. Dosing will be stratified by 2 cohorts (Cohort 1: adults with GHD irrespective of age and gender; Cohort 2: women receiving oral estrogen).

CRITERIA FOR INCLUSION AND EXCLUSION

Inclusion Criteria:

1. Female or male subjects, between 18 and 75 years (inclusive) of age, with the diagnosis of AGHD
2. Eligible subjects may be naïve to somavaratan or have previously received somavaratan in the setting of a prior Versartis study
   - Subjects naïve to somavaratan must have a documented medical history of GHD during adulthood according to the Endocrine Society guidelines[14] (confirmatory testing should be done to document persistence of childhood onset GHD into adulthood if necessary).
   - Subjects who have previously received somavaratan in the setting of a prior Versartis study can be included in this study if they have not met a stopping criterion in the corresponding study and somavaratan was well tolerated as judged by the Investigator and the Medical Monitor.
3. Naive subjects must have an IGF-I SDS value ≤ 0 at Screening
4. All subjects must agree to the contraceptive requirements outlined in Appendix 2, if applicable.
5. Female subjects of childbearing potential must have a negative pregnancy test at Screening and before Dose 1.
6. Naïve subjects who are taking any other hormone replacement therapy must have been on a stable course of treatment for at least 3 months prior to Screening (routine dose adjustments are acceptable). Subjects transitioning from other Versartis adult GHD studies and who are receiving other hormone replacement therapy may have experienced dose adjustments or initiation of treatment during their previous study and may continue treatment per standard clinical practice.
7. Naïve to somavaratan subjects currently receiving daily rhGH injections for treatment of GHD, must agree to stop taking prescribed daily rhGH therapy for the washout period of $\geq$ 14 days.
8. Underlying disorders responsible for the subject's GHD must have been clinically stable for at least 6 months prior to Screening.
9. Subjects must provide written informed consent.
10. Subjects must have a BMI (kg/m^2) between 18.0 and 40.0 (inclusive).

Exclusion Criteria:

1. Subjects with untreated adrenal insufficiency or unknown adrenal function.

   Prior Versartis study subjects will have been previously screened, however new subjects will require documentation of adrenal function via adrenal stimulation test prior to treatment. New subjects must have had an adrenal stimulation test within 3

months prior to treatment with somavaratan. Adrenal stimulation tests (as well as repeat/follow-up testing in at-risk patients) will be performed per institutional protocol.

2. Subjects with recently diagnosed thyroid dysfunction who have not started treatment or have not been stable on therapy for at least 3 months.
3. Subjects currently taking anti-inflammatory dose of glucocorticoids that could potentially compromise safety or efficacy assessments
4. Subjects currently receiving any GHRH or IGF-I product
5. Subjects with current significant cardiovascular disease, heart insufficiency of NYHA class > 2.
6. Subjects with significant comorbidities thought to increase risk of receiving growth hormone treatment or confound assessment of study outcomes (e.g. hepatic or inflammatory disorders that may affect GH-mediated hepatic IGF-I production or renal disorders that may alter somavaratan PK).
7. Subjects with a documented history of diabetes mellitus or inadequate glucose control as defined by a historical or Screening value of: FPG > 126 mg/dL (7 mM), or HbA1c ≥ 6.5%
8. Subjects with current papilledema
9. Subjects with current drug or alcohol abuse.
10. Subjects with a documented history of HIV, current HBV or HCV infection (testing not required).
11. Subjects with a history of malignancy in adulthood (subjects with a history of childhood malignancy that were subsequently treated with rhGH in childhood and remain GHD in adulthood may be enrolled).
12. Women who are pregnant or breastfeeding.
13. Subjects treated with an investigational drug other than somavaratan within 30 days prior to Screening.
14. Subjects with a significant abnormality in Screening test results as interpreted by the Investigator and/or the Medical Monitor.
15. Impossibility of or unwillingness to participate in all trial activities.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION

Somavaratan will be administered as subcutaneous injection(s) in the thigh, abdomen, upper arm or buttocks. Administration of injections will be rotated to different injection sites. Study drug may be administered by trained subjects/caregivers, or a health care professional.

A subject will be considered to have achieved a maintenance stable dose when two consecutive 7 days post-dose (Day 8, peak) IGF-I SDS values are between 0 and 2.0 SDS. Subsequently, the subject will continue to receive the maintenance dose twice-monthly (every

15 days ± 2 days). Maintenance doses may be adjusted further at the discretion of the Investigator or Medical Monitor while keeping IGF-I at 7 days post-dose between 0 and 2.0 SDS.

If a subject on a maintenance dose has an IGF-I SDS value above 2.0 SDS, dose adjustments shall be made by the Investigator or Medical Monitor based on clinical judgment with the objective to achieve and maintain IGF-I at day 7 post-dose between 0 and 2.0 SDS

The starting doses (Table 1) and Dose Titration Plan (Table 2) may be altered based on evaluation of the Phase 2 data, or ongoing evaluation of data gathered during this study. Adjustments may be implemented to alleviate safety concerns or optimize normalization of IGF-I SDS responses. The Investigator and Medical Monitor may agree to temporarily alter or suspend a subject's dose during illness or injury.

Table 1 Study Drug Starting Dose Information:

Subject Cohort Assignment	Fixed Starting Study Dose	Frequency of Administration
Cohort 1: Adults with GHD irrespective of age and gender	20 mg	Twice-Monthly
Cohort 2: Women receiving oral estrogens	40 mg	Twice-Monthly

Table 2 Dose Titration Plan

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IGF-I at Day 8	**Cohort 1**	**Cohort 2**
-1.0 to 0 SDS	4 mg dose increment	10 mg dose increment
Less than -1.0 to -2.0 SDS	10 mg dose increment	20 mg dose increment
Less than -2.0 SDS	20 mg dose increment	40 mg dose increment

1: Maximum allowable dose is 250.0 mg

DURATION OF TREATMENT

Subjects may continue on somavaratan treatment until the product is commercially available in their country or until the study is discontinued by the sponsor.

CRITERIA FOR EVALUATION – SAFETY

The following evaluations will be performed to assess study eligibility and safety:

1. Physical examination including injection site(s) evaluation.
2. Vital signs including sitting blood pressure, pulse rate, temperature and respiratory rate.
3. Laboratory tests: IGF-I, complete blood count, chemistry, fasting plasma glucose and insulin, hemoglobin A1c, thyroid function tests (Free T4 and TSH), pregnancy testing (for women of childbearing potential), lipid profile, ECGs (new subjects only), and screening anti-drug antibodies (ADAs).
4. Adverse events (AEs)
5. Concomitant medications (CMs)

Safety monitoring will continue up to approximately 60 days after a subject's final dose of somavaratan.

CRITERIA FOR EVALUATION – PHARMACODYNAMICS

Pharmacodynamic (PD) parameters include values of IGF-I and IGFBP-3. During month 1 of treatment, subjects will have IGF-I and IGFBP-3 measured every week (Day 1, Day 8, Day 16 and Day 23). After the first month and during the rest of the Titration Period, subjects will have IGF-I values measured at Day 1 (pre-dose, trough) and 7 days after dosing (Day 8, peak) of each month. During maintenance dosing PD parameters will be measured at Day 1 (pre-dose, trough) and 7 days after dosing (Day 8, peak) every three months for one year, and then every six months thereafter. Additional blood sample collection for IGF-I measures may be needed if previously stabilized subjects require further dose adjustments.

CRITERIA FOR EVALUATION – IMMUNOGENICITY

Immunogenicity will be assessed by screening for anti-drug antibodies (ADAs) at baseline and every 3 months during the first year and every 6 months thereafter. ADAs will be measured on blood samples collected at troughs (pre-dose). Testing will follow a tiered approach consisting of screening, confirmation, titration, and additional characterization of confirmed ADA positive samples.

STATISTICAL METHODS

Safety data will be listed by subject and summarized by cohort using frequencies or descriptive statistics. All subjects who receive at least one dose of somavaratan will be included in the safety analysis. Summaries of all adverse events (AEs), serious adverse events (SAEs), and incidence of Grade 3 or 4 adverse events will be classified according to severity and relationship to study drug.

No formal hypothesis testing is planned for this extension study.

For continuous variables, descriptive statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, descriptive statistics will include the number and percentage of subjects in each category.

Summaries of subject disposition, demographics, disease characteristics, and exposure and response to dosing of study medication will be provided.

Somavaratan ADAs will be summarized descriptively.

AEs, PK, and PD will also be descriptively summarized by ADA subgroup (positive, negative) to assess potential effects of ADA positivity.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	adrenocorticotropic hormone
ADA	anti-drug antibodies
AE	adverse event
AGHD	adult growth hormone deficiency
ALB	Albumin
ALT	alanine aminotransferase (SGPT)
ALP	alkaline phosphatase
ALS	acid labile subunit
ANCOVA	analysis of covariance
AST	aspartate aminotransferase (SGOT)
AUC	area under curve
BMI	body mass index
BUN	blood urea nitrogen
CA	Calcium
CFR	Code of Federal Regulations
CI	confidence interval
CM	concomitant medications
C_{max}	maximum plasma concentration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CTCAE V.4.0	Common Terminology Criteria for Adverse Events Version 4.0
CV	coefficient of variation
DP	drug product
DSMB	data and safety monitoring board
eCRF	electronic case report form
ECG	electrocardiogram

FDA	Food and Drug Administration
FPG	fasting plasma glucose
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GHD	growth hormone deficiency
GHR	growth hormone receptor
GHRH	growth hormone releasing hormone
GLP	Good Laboratory Practice
HbA1c	glycated hemoglobin
HBV	hepatitis B virus
HCV	hepatitis C virus
Hct	hematocrit
Hgb	hemoglobin
hGH	human growth hormone
HIV	human immuno-deficiency virus
HT-SDS	height standard deviation score
Hs-CRP	highly sensitivity C-reactive protein
ICH	International Conference on Harmonisation
ICF	informed consent form
IEC	independent ethics committee
IGF-I	insulin-like growth factor-I
IGF-I SDS Reference Range	IGF-I SDS range of -2.00 to 2.00
IGF-I Mean SDS Target Range	Protocol designated IGF-I SDS range of 0 to 1.50
IGF-I SDS Therapeutic Range	IGF-I SDS range of -1.50 to 1.50
IGF-I SDS	insulin-like growth factor-I standard deviation score
IGFBP-3	insulin-like growth factor-binding protein 3
IND	Investigational New Drug
IRB	Institutional Review Board

ITT	Intention to Treat
IWRS	Interactive Web Response System
K	Potassium
kDa	kilodalton
kg	Kilogram
LDL	low density lipoprotein
LDH	lactic dehydrogenase
LS	least squares
MAPK	mitogen-activated protein kinase
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mITT	modified intention To Treat
MW	molecular weight
Na	Sodium
NOAEL	no observed adverse effect level
NYHA	New York Heart Association
PD	pharmacodynamics
PGHD	pediatric growth hormone deficiency
PI	principal investigator
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetic
r	correlation coefficient
RBC	red blood cell (count)
rhGH	recombinant human growth hormone
SAE	serious adverse event
SC	subcutaneous

SD	standard deviation
SDS	standard deviation score
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (AST)
SGPT	serum glutamic pyruvic transaminase (ALT)
SOP	standard operating procedure
SRC	safety review committee
STAT	signal transducer and activator of transcription
SUSAR	suspected, unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half life
T4	Thyroxine
TEAE	treatment emergent adverse event
T_{max}	time to maximum plasma concentration
TSH	thyroid stimulating hormone
US	United States
WBC	white blood cell (count)
WHO	World Health Organization
WHODDE	WHO Drug Dictionary Enhanced
µg	microgram

Rationale for the Proposed Changes to Protocol 15VR8

The main objectives of this protocol revision (Version 2) are to introduce modifications to the starting doses, dose frequency, continued dosing in rollover subjects, and dose titration plan used in the study. Somavaratan is being investigated as a once-monthly SC injection in adults with GHD in a Phase 2 study (Protocol 15VR7), where one of the objectives is the assessment of the starting dose and the dose titration plan. This open label extension study (Protocol 15VR8) is open to any subjects that complete a Versartis somavaratan study, as well as up to 40 new adult subjects with GHD.

At an initial starting dose of 0.6 to 1.0 mg/kg in the Phase 2 study, IGF-I levels 7 days after the first dose were > 2.0 SDS in 19/36 subjects (53%) and > 3.0 SDS in 14/36 subjects (39%). These IGF-I values were transient and not accompanied by clinically important adverse events.

Despite dose adjustments (reductions), of the 29 subjects that completed 5 doses in the Phase 2 study at the time of this protocol amendment, IGF-I values 7 days after the last (fifth) dose were > 2.0 SDS in 16 subjects (55%) and > 3.0 SDS in 7 subjects (24%).

Based on these findings, it was determined that:

- A lower starting dose is needed
- The maintenance doses in rollover subjects seems to be too high, and a lower maintenance dose is needed
- The dose titration plan was not adequate to address the high IGF-I levels at Day 8 and a new titration plan based solely on IGF-I SDS 7 days after dosing is proposed
- The dosing frequency should be revised to twice-monthly to allow for adequate response during the dosing interval with reduced IGF-I excursions above 2.0 SDS
- Dosing initiation and titration should be made on a fixed (mg) basis and not be based upon-body weight adjusted (mg/kg) basis

Starting Dose

Evaluation of the doses resulting in Day 8 IGF-I above and below 2.0 SDS indicate that for adult subjects with GHD (except women receiving estrogens), 20 mg was the lowest dose that did not result in a response > 2.0 SDS in 90% of the subjects For women receiving estrogens, a similar analysis was performed and the identified starting dose was 40 mg.

A fixed starting dose regardless of weight, age and gender is therefore planned for this study:

- 20 mg for all subjects other than women receiving oral estrogen
- 40 mg for women receiving oral estrogen

Dosing Frequency

Data from the ongoing analysis of the Phase 2 study have shown that the pre-dose (trough) IGF-I levels were similar to the baseline IGF-I levels (prior to any somavaratan exposure), suggesting that the duration of effect was less than one month. In addition, after the last (fifth) dose of somavaratan in the Phase 2 study, IGF-I levels at 21 days after dosing had already diminished to values not different than the pre-dose levels. Based on this analysis, the planned dosing frequency for this study is:

- Twice-Monthly

Continued Dosing in Rollover Subjects Presently Participating in This Study

As previously described, approximately 50% of the subjects who completed the 15VR7 study and rolled over to the 15VR8 protocol still have high IGF-I levels 7 days after somavaratan administration (Day 8). A lower dose is needed to prevent the transient IGF-I excursions. For rollover subjects, it is proposed that the current once monthly dose they are receiving will be divided in 2, and rounded down to the nearest even number (minimum dose 20 mg, 40 mg for women on oral estrogen) and administered twice-monthly (example: current dose is 54 mg, divided by two = 27 mg, rounded down to nearest even number = 26 mg. The subject will begin to receive somavaratan 26 mg twice-monthly).

Titration Plan

The titration plan will be modified to be based exclusively on IGF-I at Day 8, which represents the sampling point of the highest response to Somavaratan. The objective of the new titration plan is to achieve an IGF-I at Day 8 within 0 and 2.0 SDS while ensuring that the IGF-I response does not exceed 2.0 SDS.

After subjects achieve maintenance dosing (two consecutive IGF-I at Day 8 within target range under the same dose) doses may be modified based on the Investigator or Medical Monitor clinical judgment with the goal to maintain IGF-I SDS at Day 8 within target range (0 to 2.0).

Summary of the Proposed Changes to Version 2 of Protocol 15VR8

Synopsis

- Updated Objective section to include as a secondary objective to evaluate the dose (starting and maintenance) and the dose titration plan of twice-monthly somavaratan during long-term treatment
- Updated **Study Design** section to describe the twice-monthly dosing regimen, starting doses and treatment cohorts
- Updated the **Inclusion/Exclusion Criteria** to indicate that new naïve to somavaratan treatment subjects must agree to a wash out period of minimum 14 days and have a screening IGF-I SDS < 0
- Updated the **Test Product, Dose and Mode of Administration** section indicating the new dosing regimen and dose titration for all subjects based on the Day 8 IGF-I SDS. Updated the Dose Titration Plan (Table 2)

Updated Section 3.1, **Overall Study Design and Plan** to describe:

- The twice-monthly dosing regimen and starting doses that will be used for all subjects
- The visit schedule all subjects will follow
- The dosing cohorts that will be used in the study
- The Dose Titration Plan (Table 2)

Updated Section 3.7, **Inclusion Criteria**:

- **Criterion # 2** describes the eligible subjects that may enroll in the study
- **Criterion # 3** describes the requirement that new naïve to somavaratan subjects entering the study must have a screening IGF-I SDS < 0
- **Criterion # 7 describes the requirement that new n**aïve to somavaratan subjects currently receiving daily rhGH injections for treatment of GHD, must agree to stop taking prescribed daily rhGH therapy for the washout period of ≥ 14 days

Updated Section 4, **Study Treatments**:

- This section has been revised to describe the starting doses, dose titration plan, introduction of the somavaratan autoinjector device, treatment groups, and dose schedule for all subjects

Updated Section 6, **Study Activities**:

- This section has been updated to describe the activities for all subjects that will occur during Screening and in the first month of treatment as well as during the monthly dose titration

Updated **Appendix 1**, **Schedule of Events**:

- Appendix 1 revised to describe the activities for all subjects enrolled in the study

1 INTRODUCTION

Somavaratan is an investigational recombinant human growth hormone (rhGH) analog, designed to maintain active drug levels for a longer period of time than currently available therapies. It is being developed for treatment of growth hormone deficiency (GHD) in adults and children. Somavaratan is a novel fusion protein (MW 119 kDa) consisting of recombinant human growth hormone (rhGH) and two sequences (XTEN) of hydrophilic amino acids: one sequence attached to the N- and one to the C-terminus of rhGH. The N-terminus XTEN domain enables half-life extension of the rhGH by increasing the hydrodynamic diameter and molecular weight of rhGH, which reduces kidney filtration. The C-terminus XTEN domain may also enable half-life extension of the rhGH by delaying receptor mediated clearance.[2,3] Somavaratan is being developed as a long-acting alternative to daily rhGH injections. Daily rhGH is currently the only available treatment in the United States, Canada and Europe for adults and children with growth hormone deficiency. Human growth hormone (hGH) is naturally secreted from the human anterior pituitary as intermittent pulses lasting from minutes to hours, typically occurring during sleep. To promote anabolic and growth processes, hGH binds to the hGH receptor initiating signaling processes involving the STAT (signal transducer and activator of transcription), the MAPK (mitogen-activated protein kinase) and the PI3K (phosphoinositide-3 kinase) pathways. Insulin-like growth factor-I (IGF-I) gene expression is activated from hGH receptor signaling resulting in secretion of IGF-I into the circulation. Although hGH retains unique biological actions, IGF-I is the primary mediator for the growth promoting effects of hGH. [4,5] As such, IGF-I also serves as the primary pharmacodynamic (PD) marker for response to rhGH administration. In the circulation, IGF-I forms a complex with insulin-like growth factor binding protein-3 (IGFBP-3) and the acid labile subunit (ALS). Both IGFBP-3 and ALS expression are also regulated by hGH receptor activation.

GHD occurs in children and adults and results from a variety of genetic, neoplastic, inflammatory, traumatic and iatrogenic causes.[6] The consequences of GHD will depend on the severity of the deficiency and the age at which the deficiency occurs. Subjects with untreated childhood onset GHD will have significant growth failure with attainment of adult heights significantly less than five feet in many instances.[7] In addition, there is abnormal body composition with decreased bone mineralization, decreased lean body mass and increased fat mass. In children, treatment with exogenous rhGH promotes normal body composition and initiates a period of accelerated or “catch-up” growth that when begun at an early age allows attainment of normal adult height.[7,8,9,10,11]

GHD is also a well-recognized clinical syndrome in adults. In the adult, GHD may be a continuation of the childhood-onset condition or result from damage to the pituitary during adult life. Manifestations of the adult GHD syndrome include altered body composition (decreased muscle mass, increased fat mass, osteopenia), alterations in glucose and lipid metabolism leading

to increased risk for adverse cardiovascular events, decreased exercise capacity and decreased quality of life. [12,13,14]

Beginning in 1985, national health authorities have approved the use of rhGH as a therapy for children with GHD.[19,20,21,22,23] In the years after this initial approval, adult GHD and a wide array of conditions adversely affecting the growth of children were also approved. In GHD patients, exogenous administration of rhGH can reverse the clinical consequences caused by deficiencies in endogenous hGH secretion.

Daily subcutaneous dosing of rhGH is the currently approved therapy for the replacement of insufficient endogenous secretion of GH. It is important to note that daily rhGH therapy does not mimic the typical endogenous pulsatile release of GH in healthy individuals. However, daily injections of rhGH have been demonstrated for over 30 years to be a safe and effective therapy for treatment of GHD. Clinical studies of continuous infusion of rhGH with a pump demonstrate comparable metabolic effects, growth velocity, and IGF-I responses to those achieved with daily rhGH injections.[16,17,18] A continuous infusion of rhGH has been compared to daily rhGH therapy in adult GHD patients for 6 months and in GHD children for 6 months).[30,18] These studies indicated that the safety profile and effects on the IGF-I responses were not significantly different between patients treated with continuous subcutaneous infusion of rhGH or once daily subcutaneous rhGH therapy. Therefore, continuous, as well as daily, administration of rhGH, neither of which follow endogenous secretion patterns, appear to be safe and efficacious. There is no preventative therapy for GHD and no other treatment modalities are known to be effective.

Daily injections can be a challenge, and a lack of compliance with daily rhGH administration is commonplace and can lead to loss of treatment effects.[24,25,26] Additionally, many adult GHD patients choose not to initiate therapy due to the onus of daily injections, thereby missing the opportunity to mitigate the cardiometabolic risks associated with GHD.[29] Long-acting rhGH offers the possibilities of fewer injections, enhanced compliance and attainment of improved treatment outcomes.

Clinical Experience

1.1.1 Adult Growth Hormone Deficiency

The first in human study of somavaratan was a randomized, placebo controlled, single ascending dose study of 5 active dosing groups in 50 adult subjects with documented GHD (Protocol 11VR1.1). Somavaratan doses of 0.05, 0.10, 0.20, 0.40, or 0.80 mg/kg were given as a single subcutaneous (SC) dose.[27] Each of the five dosing arms consisted of 8 subjects randomized to active drug and 2 subjects to placebo. Blood samples for PK and PD determinations were obtained at 21 time points over 30 days. The amplitude and duration of IGF-I exposure was directly proportional to the somavaratan dose. IGF-I SDS was normalized for a mean of approximately three weeks for the 0.80 mg/kg group. Time to maximum concentration of IGF-I

in this group was 5.1 ± 2.0 days. Safety monitoring was carried out for 60 days post-dose. Stopping rules were pre-specified by protocol. The membership and activities of the Safety Review Committee (SRC) were specified in the SRC Charter, developed prior to study onset. SRC meetings were conducted prior to each dose escalation; no stopping criteria were met at any time point.

In Protocol 11VR1.1, single doses of somavaratan in adults with GHD were safe and well tolerated. There were no serious or unexpected adverse events (AEs). There was no lipoatrophy or nodule formation at the injection sites. There were no laboratory safety signals. All subjects completed the study.

Single somavaratan doses safely increased the amplitude and duration of IGF-I in a dose-dependent manner. After a single 0.80 mg/kg dose, mean IGF-I SDS was maintained in the *therapeutic* range (greater than -1.50 SDS) for a mean of three weeks. At 0.80 mg/kg, somavaratan had a mean terminal elimination half-life ($t_{1/2}$) of 131 hours, 30-60 times longer than reported for daily rhGH in approved product package inserts.[27] Prolonged IGF-I responses were achieved without meaningful overexposure to IGF-I. The pharmacokinetics and pharmacodynamics combined with the observed safety profile indicate the potential for safe and effective monthly dosing.[27]

1.1.2 Pediatric Growth Hormone Deficiency

The safety and efficacy of somavaratan in naïve to treatment, pre-pubertal subjects with GHD was demonstrated in the Phase 1b/2a study (Protocol 12VR2). Somavaratan was safe and well tolerated with an overall safety profile similar to daily rhGH. Discomfort at the injection site was the most frequent related adverse event, and occurred in less than half the subjects over 6 months and was mild (Grade 1) and transient (< 30 minutes in 90% of the subjects). After more than 1300 injections, inspection of the injection sites revealed only six instances of mild, transient erythema, and no nodule formation or lipoatrophy was observed. The PK of somavaratan exhibited dose proportionality. As expected from the Phase 1b PK model, the weekly dosing regimen resulted in an increased level of somavaratan until steady state was reached after the third dose, and the twice-monthly and once-monthly dose regimens did not result in drug accumulation after 6 months. The IGF-I responses were maintained over each of the dosing intervals. The changes of IGF-I matched the predicted changes from the PK/PD model of the Phase 1b results. No meaningful overexposure to IGF-I occurred with only six transient IGF-I SDS values above 2.0 and none above 2.60 (all in the once-monthly cohort where the total monthly dose of 5.0 mg/kg somavaratan was administered). Over 6 months, substantial improvements were noted in height standard deviation scores and mean annualized 6 month height velocities were similar to annual height velocities for published historical controls (matched for age and severity of GHD) receiving 33 µg/kg rhGH daily[15]. There was no undue advancement of skeletal age (bone age). Overall, somavaratan appears to provide comparable

safety and efficacy to historical studies of daily rhGH with the potential to reduce dose administration to weekly, twice-monthly or monthly.

In Phase 1b, 48 pre-pubertal, naïve to treatment children received a single SC dose of somavaratan. GHD was diagnosed by medical history, auxology and two growth hormone stimulation tests. In ascending order, subjects received somavaratan doses of 0.80, 1.20, 1.80, 2.70, 4.00, or 6.00 mg/kg. Blood samples for PK/PD determinations were obtained at 6 time points over 30 days. Safety monitoring was carried out for 60 days post-dose. Stopping rules were specified by protocol. The membership and activities of the SRC were specified in the SRC Charter, developed prior to study onset. SRC meetings were conducted prior to each dose escalation; no stopping criteria were met at any time point.

In GHD children, single dose somavaratan over the specified dose range was safe and well tolerated. A minority of subjects reported any drug-related AE. Reported AEs were mild (Common Terminology Criteria for Adverse Events, CTCAE V.4.0 Grade 1), transient, and of the type generally observed when starting rhGH in children, including discomfort at the injection site, headache, myalgia, pain in an extremity and increased appetite. No serious or unexpected AEs were reported. There were no laboratory safety signals. Nodule formation and lipoatrophy at injection sites were not reported. All 48 subjects completed the study.

After subcutaneous administration to GHD children, somavaratan is rapidly absorbed achieving a maximum plasma concentration (C_{max}) in 2 to 3 days after dosing, similar to that observed in GHD adults.[27] Because sparse sampling is used in small children, the number of sample time points did not allow for an accurate determination of terminal elimination half-lives. However, as noted in GHD adults, substantial somavaratan concentrations were observed 30 days after injection.

IGF-I was the primary PD marker for this study. The normal range for IGF-I in children varies greatly with age, with mean values more than doubling during childhood. Accordingly, IGF-I responses were described as IGF-I standard deviation scores (IGF-I SDS) calculated from IGF-I concentrations as (Subject IGF-I – mean IGF-I for age)/IGF-I SD for age. All subjects had relative IGF-I deficiency at Baseline (IGF-I SDS < -1.0) and the increase from Baseline in the 30 day average IGF-I SDS was proportional to dose. There were no IGF-I SDS values ≥ 3 and only two subjects had an IGF-I level above the normal range (IGF-I SDS > 2.0). In these two subjects, IGF-I SDS returned to the normal range by the next sampling time point.

The enrollment of the Phase 2a portion of Protocol 12VR2 was completed with 64 pre-pubertal GHD children randomized in 3 dosing arms: 1.15 mg/kg weekly, 2.5 mg/kg twice-monthly, and 5.0 mg/kg once-monthly. Sixty-three (63) of 64 subjects completed the 6 month study. Somavaratan was safe and well tolerated. The most frequent adverse event was mild, transient (< 30 minutes) injection site discomfort and was reported as two events or less for

80% of the subjects over 6 months. Remaining adverse events were also mild and transient, occurred infrequently (< 10% of subjects), and included events typically observed during initiation of daily rhGH (e.g., headache, pain in extremities). No related serious adverse events (SAEs), unexpected adverse events, lipoatrophy at injection sites or signs of increased intracranial pressure occurred.

Mean IGF-I responses persisted over each of the dosing intervals and individual IGF-I SDS exceeded 2.0 (maximum of 2.6) in only 5 subjects. Averaged over seven sampling times in 6 months, the Phase 2a dosing regimens resulted in mean IGF-I SD scores slightly below the mean for age matched children (mean average IGF-I SDS = -0.6). Over each dose interval, the IGF-I SDS was maintained above Baseline on average. There were no significant changes in successive IGF-I peaks or troughs indicating no accumulation of IGF-I response or evidence of desensitization or down-regulation of the GHR. Improvements in height standard deviation score and height velocity were noted in all three dosing arms. The mean annualized height velocity for the twice-monthly regimen of somavaratan was 8.6 cm/year as compared to 8.3 cm/year for age-matched historical controls taking a daily rhGH.[15]

Immunogenicity was assessed at 4 time points in Phase 1b, at three time points in Phase 2a, and at 3 time points in the Extension Study in all pediatric subjects enrolled in these two studies by measuring anti-somavaratan antibodies (anti-drug antibodies, ADA) in serum samples. The serum from all ADA-positive subjects was further characterized using an *in vitro* cell assay that determines if the serum sample can inhibit human growth hormone (hGH) stimulated cell proliferation.

ADAs were first observed at Month 3 and remained consistent at Months 6, 12 and 18. Analyses have been performed on Month 18 data to determine if ADA positive and negative subjects differed with respect to clinical endpoints. ADA status had no statistically significant effect on the incidence or type of related adverse events, height velocity, drug concentrations, IGF-I responses or IGFBP-3 responses. The serum from several ADA-positive subjects tested positive for the ability to inhibit hGH in an *in vitro* cell proliferation assay. However, there were too few subjects that showed *in vitro* cell inhibition to conduct meaningful analysis of the significance of these results on clinical endpoints.

1.1.3 Summary of Clinical Experience

The safety, tolerability and PK/PD responses to somavaratan have been studied in 108 subjects with documented GHD (40 adults, 68 children). Somavaratan is intended for use as a long acting rhGH. When administered in children as weekly, twice-monthly or monthly doses, somavaratan was safe and well tolerated as indicated by the low number of drug-related AEs that were mild, transient and of the type expected with growth hormone replacement. No new safety signals have emerged for somavaratan. In adults as well as children, drug exposure parameters (C_{max} and AUC) were proportional to dose. The ability of single dose somavaratan to significantly

increase IGF-I exposures for up to one month was demonstrated in both GHD children and GHD adults. Normalization of IGF-I exposures did not result in meaningful overexposure to IGF-I. In all, only 6 adults and 5 children had IGF-I levels above the normal range (IGF-I SDS > 2.0). These responses were transient and no pediatric subject had an average 30 day IGF-I exposure above the normal range during 6 months of treatment. As anticipated from prior experience with daily rhGH, the somavaratan dose required to normalize IGF-I was demonstrated to be higher in children than in adults.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is:

- To evaluate the safety of somavaratan during long-term treatment in adults with GHD

2.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the dose (starting and maintenance) and the dose titration plan of twice-monthly somavaratan during long-term treatment
- To evaluate the immunogenicity of somavaratan during long-term treatment in adults with GHD by detection and characterization of anti-somavaratan antibodies (anti-drug antibodies, ADAs)
- To evaluate pharmacodynamic (PD) responses (IGF-I, IGFBP-3) during long-term somavaratan treatment

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This open-label extension study will evaluate the safety of long-term twice-monthly administration of somavaratan in adults with GHD. This study is open to subjects completing a Versartis adult GHD study as well as approximately 40 new somavaratan naïve subjects (either rhGH treatment naïve or currently receiving daily rhGH therapy). A total of up to 250 subjects may be enrolled in this study. All subjects will receive twice-monthly (every 15 days ± 2 days) subcutaneous (SC) somavaratan. All subjects will have somavaratan doses titrated per the Dose Titration Plan (Table 2) to each subject's individual IGF-I responses based on the IGF-I level collected 7 days post-dose (Day 8) until a maintenance dose is achieved. Maintenance dose is defined as an IGF-I value between 0 and 2.0 SDS for two consecutive 7 day post-dose time points (peak).

Subjects receiving somavaratan once-monthly in this study (Protocol 15VR8) or in a previous somavaratan study (Protocol 15VR7), will have their dose decreased by half (minimum dose of 20 mg, 40 mg for women on estrogen, rounded down the nearest even number) and will be titrated per the Dose Titration Plan (Table2).

New subjects naïve to somavaratan treatment enrolling in this study will be assigned to one of two cohorts and will receive a starting dose of 20 mg twice-monthly (40 mg for women on estrogen) (Table 1) and will be titrated per the Dose Titration Plan (Table 2).

Maintenance doses may be adjusted further at the discretion of the Investigator or Medical Monitor while maintaining IGF-I at Day 8 (7 days post dose) within target range. For patients on maintenance dose that have IGF-I levels > 2.0 SDS at any point during the maintenance period, dose adjustment shall be made by the Investigator or Medical Monitor based on clinical judgment with the objective to achieve and maintain IGF-I at day 7 post-dose between 0 and 2.0 SDS. Any change in somavaratan dose in a subject that has achieved maintenance dosing will be followed by an ad-hoc Day 8 IGF-I measurement to ensure IGF-I values are within target range (0 and 2.0 SDS).

Study visits/blood sample collections will occur every week during the first month of the study, followed by monthly clinic visits until the subject has reached maintenance dose. Once maintenance dose is achieved, in clinic visits will occur quarterly during the first year. Although quarterly visits will continue throughout the study, after the first year blood samples will be collected every 6 months, with intervening visits used for brief physical exams and collection of AEs and concomitant medications.

In current clinical practice with daily rhGH products, individualized dose titration is the standard of care. Daily rhGH doses are titrated to achieve normalization of IGF-I (the primary PD parameter) without jeopardizing safety. Each patient may have different IGF-I and safety

responses to daily rhGH treatment, especially with regards to potential adverse events such as edema. The IGF-I response to rhGH depends on many factors. One of the mostly recognized is the exposure to estrogens, in particular oral estrogens, which confers relative resistance to rhGH. Consequently, subjects will be stratified into the following two cohorts:

- Cohort 1: adults with GHD irrespective of age and gender will receive a starting dose of 20 mg twice-monthly
- Cohort 2: women receiving oral estrogen will receive a starting dose of 40 mg twice-monthly

Subjects entering the study currently receiving daily rhGH treatment must have discontinued rhGH for a minimum of 14 days prior to initiating treatment with somavaratan. Additionally, these subjects must have a baseline IGF-I SDS ≤ 0.

Doses will be scheduled relative to Day 1, not relative to the prior dose, and will be administered every 15 days ± 2 days, unless a dose outside of this time window is approved by the Medical Monitor. During dose titration, all monthly Day 1 adjusted somavaratan doses will be administered in clinic. Other doses (Day 16) may be administered in clinic during study visits by a qualified healthcare professional, or at home by a trained subject/caregiver. Dose titration requires weekly blood sample collection during the first month to monitor IGF-I response with Day 1 (pre dose, trough) and Day 8 (peak) blood sample collection during the monthly titration visits. Once dose stabilization is achieved, blood samples will be collected quarterly during the first year. Although quarterly visits will continue throughout the study, after the first year blood samples will be collected every 6 months, with intervening visits used for brief physical exams and collection of AEs and concomitant medications.

For new subjects, treatment is initiated at the fixed starting dose (20 mg or 40 mg, as per assigned cohort), with subsequent doses determined based on individual IGF-I response. IGF-I levels (ng/mL) will be checked at pre-dose (trough) and at 7 (±1) days after dosing (Day 8, peak) until dose stabilization is achieved. The 7 day post-dose (Day 8, peak) IGF-I SDS value will be used to determine dose adjustments with a target range of 0 to 2.0 SDS. If the peak IGF-I SDS is below the target range (e.g., < 0 SDS), the dose shall be titrated up according to the Dose Titration Plan (Table 2). If the peak IGF-I SDS is above the target range (e.g., > 2.0 SDS), the dose shall be titrated down according to the Dose Titration Plan (Table 2). Once a subject has achieved an IGF-I SDS within the target range for two consecutive months, s/he will be considered dose stabilized and will continue to receive that maintenance dose for the remainder of the study unless further adjustment becomes necessary. After dose stabilization is achieved, IGF-I levels will no longer be tested monthly; maintenance subjects will have pre-dose and 7 days post-dose IGF-I levels drawn every 3 months for the first year, and then every 6 months thereafter. If a subject on maintenance dose has an IGF-I value outside the target range, further dose adjustments will be considered on an individual basis by the Investigator or Medical Monitor with the objective to achieve and maintain IGF-I SDS at Day 8 within target range

(IGF-I SDS 0 - 2.0). Any change in somavaratan dose in a subject that has achieved maintenance dosing will be followed by an ad-hoc Day 8 IGF-I measurement to ensure IGF-I values are within target range (0 and 2.0 SDS).

Subjects will be monitored for safety throughout their participation in the study. Safety will be monitored by physical examination, inspection of injection sites, vital signs, , clinical laboratory determinations (including complete blood count, chemistry, lipid profile, urinalysis, measurements of adrenal function, thyroid function, and glucose metabolism), ECG's (new subjects only), and immunogenicity assessments. Immunogenicity assessments will include anti-drug antibodies (ADA). All ADA positive samples will be characterized in an *in vitro* cell assay that determines if the serum sample can inhibit human growth hormone (hGH)-stimulated cell proliferation.

Adverse events (AEs) and concomitant medications (CMs) will be captured throughout the study. AEs will be coded using MedDRA dictionary (v 18.0) and summarized using the coded terms; and CMs will be coded using the WHO Drug dictionary (WHODDE [WHO Drug Dictionary Enhanced]). Summaries of all treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be presented. The incidence of Common Terminology Criteria for Adverse Events (v 4.0) Grade 3 or 4 will be classified according to severity and relationship to study drug.

3.2 Rationale for Study Design

The purpose of this open label extension study is to evaluate the long-term safety of twice-monthly somavaratan subcutaneous dosing in adults with GHD.

There are currently no preventative treatments for GHD in children or adults. GH replacement therapy provides positive effects on body composition, lipid metabolism, bone metabolism, and quality of life in adults with GHD. Because the only currently available treatment is daily rhGH, compliance is an important barrier to these benefits; patients either missing doses or opting to forego treatment altogether due to the burden of daily injections.[29,31] Somavaratan is being developed for twice-monthly dosing in GHD adults to provide an alternative to daily dosing that may avoid these compliance and adherence problems and attendant loss of treatment effect.

3.3 Dose Selection

The current standard of care for adult subjects with GHD who are being treated with daily rhGH is to initiate therapy at a low dose of rhGH (e.g., 2 µg/kg/day) and then titrate the dose up or down based on IGF-I measurements (the primary PD parameter) and the presence or absence of adverse events. Each subject may have different IGF-I and safety responses to rhGH treatment, especially with regards to potential adverse events such as edema. Consequently, somavaratan dosing will also be titrated to an individual's IGF-I SDS response with the aim of safely achieving normalization of IGF-I SDS.

The doses subjects receive in this study will be based on the evaluation of data obtained in the Phase 2 study and on oral estrogen use, because women using oral estrogens are less sensitive to rhGH.[28,29] Section 4 describes somavaratan treatment in detail.

3.4 Study Duration and Dates

This study is a long-term evaluation of somavaratan administered twice-monthly. Subjects may continue on somavaratan treatment until the product is commercially available in their country or until the study is discontinued by the sponsor.

3.5 Safety Review and Stopping Rules

Subjects will be monitored for safety throughout their participation in the study. Safety will be monitored by physical examination, inspection of injection sites, vital signs, clinical laboratory determinations, PK/PD assessments, and immunogenicity assessments. AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE v 4.0). AEs will be coded using the MedDRA dictionary and CMs using the WHO Drug dictionary.

An external data and safety monitoring board (DSMB) will monitor and protect the safety of the study subjects throughout the study duration. DSMB meetings will occur twice yearly (approximately every 6 months).

In accordance with the DSMB Charter, summaries of data will be prepared by the project statistician. The data for review will be outlined in the DSMB charter and will be agreed to in advance by the DSMB members.

The DSMB may recommend modifications of the protocol to enhance subject safety and to recommend early termination of the study if there is strong evidence that somavaratan poses a safety concern to subjects in the study.

3.5.1 Stopping Rules

The Stopping Criteria include:

1. The Principal Investigator (PI) and/or Medical Monitor conclude it is unsafe or not in the subject's best interest to continue.
2. IGF-I SDS $\geq$ 3.0 SDS on two consecutive Day 8 time points despite dose adjustments
3. IGF-I SDS $\geq$ 2.0 SDS on two consecutive Day 8 time points despite dose adjustments and accompanied by clinically meaningful drug-related AEs, as determined by the Investigator and the Medical Monitor.

Subjects meeting individual stopping criteria will be withdrawn from the study.

The Stopping Criteria for a dosing cohort or the study include the determination that the dosing cohort or the study is unsafe to continue.

STUDY POPULATION SELECTION

3.6 Study Population

The study population will consist of adults age 18-75 years (inclusive) who have well-established growth hormone deficiency (GHD) according to the Endocrine Society guidelines.[14] A total of up to 250 subjects may be enrolled. Eligible subjects will have completed a Versartis adult GHD study or will be included as new subjects who are either rhGH treatment naïve or transitioned from daily rhGH therapy to twice-monthly somavaratan. New subjects receiving daily rhGH treatment must discontinue daily rhGH use for a minimum of 14 days prior to somavaratan dosing.

3.7 Inclusion Criteria:

Eligible subjects must meet all inclusion criteria.

1. Female or male subjects, between 18 and 75 years (inclusive) of age, with the diagnosis of AGHD.
2. Eligible subjects may be naïve to somavaratan or have previously received somavaratan in the setting of a prior Versartis study.
   - Subjects naïve to somavaratan must have a documented medical history of GHD during adulthood according to the Endocrine Society guidelines[14] (confirmatory testing should be done to document persistence of childhood onset GHD into adulthood if necessary)
   - Subjects who have previously received somavaratan in the setting of a prior Versartis study can be included in this study if they have not met a stopping criteria in the corresponding study and somavaratan was well tolerated as judged by the Investigator and the Medical Monitor
3. Naive to somavaratan subjects must have an IGF-I SDS value ≤ 0 at Screening (inclusive).
4. All subjects must agree to the contraceptive requirements outlined in Appendix 3, if applicable.
5. Female subjects of childbearing potential must have a negative pregnancy test at Screening and on Day 1.
6. Naïve subjects who are taking any other hormone replacement therapy must have been on a stable course of treatment for at least 3 months prior to Screening (routine dose adjustments are acceptable). Subjects transitioning from other Versartis adult GHD studies and who are receiving other hormone replacement therapy may have experienced dose adjustments or initiation of treatment during their previous study and may continue treatment per standard clinical practice.

7. Naïve subjects currently receiving daily recombinant human growth hormone (rhGH) injections for treatment of GHD, must agree to stop taking prescribed daily rhGH therapy for the washout period of ≥ 14 days.
8. Underlying disorders responsible for the subject's GHD must have been clinically stable for at least 6 months prior to Screening.
9. Subjects must provide written informed consent.
10. Subjects must have a BMI (kg/m2) between 18.0 and 40.0 (inclusive).

3.8 Exclusion Criteria:

Subjects with the following conditions/criteria will be excluded.

1. Subjects with untreated adrenal insufficiency or unknown adrenal function. Prior Versartis study subjects will have been previously screened, however new subjects will require documentation of adrenal function via adrenal stimulation test prior to treatment. New subjects must have had an adrenal stimulation test within 3 months prior to treatment with somavaratan. Adrenal stimulation tests (as well as repeat/follow-up testing in at-risk patients) will be performed per institutional protocol.
2. Subjects with recently diagnosed thyroid dysfunction who have not started treatment or have not been stable on therapy for at least 3 months.
3. Subjects currently taking anti-inflammatory dose of glucocorticoids that could potentially compromise safety or efficacy assessments.
4. Subjects currently receiving any GHRH or IGF-I product.
5. Subjects with current significant cardiovascular disease, heart insufficiency of NYHA class > 2.
6. Subjects with significant comorbidities thought to increase risk of receiving growth hormone treatment or confound assessment of study outcomes (e.g. hepatic or inflammatory disorders that may affect GH-mediated hepatic IGF-I production or renal disorders that may alter somavaratan PK).
7. Subjects with a documented history of diabetes mellitus or inadequate glucose control as defined by a historical or Screening value of: FPG > 126 mg/dL (7 mM), or HbA1c ≥ 6.5%.
8. Subjects with current papilledema.
9. Subjects with current drug or alcohol abuse.
10. Subjects with a documented history of HIV, current HBV or HCV infection (testing not required).
11. Subjects with a history of malignancy in adulthood (subjects with a history of childhood malignancy that were subsequently treated with rhGH in childhood and remain GHD in adulthood may be enrolled).

12. Women who are pregnant or breastfeeding.
13. Subjects treated with an investigational drug other than somavaratan within 30 days prior to Screening.
14. Subjects with a significant abnormality in Screening test results as interpreted by the Investigator and the Medical Monitor.
15. Impossibility of or unwillingness to participate in all trial activities.

3.9 Subject Withdrawals and Replacements

Consent may be withdrawn at any time for any reason by a subject without prejudice to future treatment. The Investigator or Medical Monitor may withdraw a subject if it is judged to be in the best interest of the subject or if it is clear the subject cannot comply with the protocol.

Subjects that develop a new significant medical condition at any point during the study may be withdrawn. Subject numbers will not be re-assigned. Subjects will not be replaced.

4 STUDY TREATMENT(S)

4.1 Description of Treatment(s)

4.1.1 Somavaratan Treatment

Somavaratan will be provided either in a vial and syringe configuration or as an autoinjector device (when available) and administered as subcutaneous injection(s) in the thigh, abdomen, upper arm or buttocks. Injection sites shall be rotated. Study drug may be administered by trained subjects/caregivers, or a health care professional.

Somavaratan is formulated at a nominal concentration of 100 mg/mL in 20 mM histidine, 154 mM sodium chloride, pH 5.5. Somavaratan is a colorless, clear liquid, free from visible particles. See Section 4.2 for starting dosages.

4.2 Treatments Administered

All subjects will receive somavaratan twice-monthly.

- Subjects receiving somavaratan once monthly in a prior Versartis adult GHD study or in this study, irrespective of the cohort assignment and whether they have achieved maintenance dosing, will transition to receive treatment at half of their current dose (rounded down to the nearest even number, minimum dose of 20 mg).

- New subjects naïve to somavaratan will be assigned to one of two treatment cohorts (Table 1) with different starting doses based on the subject's use of oral estrogens. The initial dose will be a fixed dose.

All subjects will have Day 8 IGF-I SDS evaluated each month with subsequent dose adjustments made per the Dose Titration Plan (Table 2).

Table 1 Study Drug Starting Dose Information

Subject Cohort Assignment	Fixed Starting Study Dose	Frequency of Administration
Cohort 1: Adults with GHD irrespective of age and gender	20 mg	Twice-Monthly[1]
Cohort 2: Women receiving oral estrogens	40 mg	Twice-Monthly[1]

1: Allowable dosing window is every 15 days ± 2 days

Table 2 Dose Titration Plan

Downward Dose Titration		
IGF-I at Day 8	**Cohort 1**	**Cohort 2**
0 to 2.0 SDS	No change in dosing	No change in dosing
2.01 to 3.0 SDS	4 mg dose decrement	4 mg dose decrement
Greater than 3.0 SDS	10 mg dose decrement	10 mg dose decrement
Upward Dose Titration[1]		
IGF-I at Day 8	**Cohort 1**	**Cohort 2**
-1.0 to 0 SDS	4 mg dose increment	10 mg dose increment
-1.0 to -2.0 SDS	10 mg dose increment	20 mg dose increment
Less than -2.0 SDS	20 mg dose increment	40 mg dose increment

1: Maximum allowable dose is 250.0 mg

The starting doses and Dose Titration Plan (Tables 1 and 2) may be altered by the Sponsor based on continued evaluation of the Phase 2 data and/or data gathered during this study. Adjustments may be implemented to alleviate safety concerns or optimize normalization of IGF-I SDS responses. The Investigator and Medical Monitor may agree to temporarily alter or suspend a subject's dose during illness or injury.

If a subject on maintenance dose has an IGF-I value outside the target range, further dose adjustments will be considered on an individual basis by the Investigator or Medical Monitor with the objective to achieve and maintain IGF-I SDS at Day 8 within target range (IGF-I SDS between 0 - 2.0)

4.3 Selection and Timing of Dose for Each Subject

The Medical Monitor will review results of all available medical history and Screening activities and notify the Investigator and Premier (the CRO) if the subject may be enrolled in the study.

Subjects will receive somavaratan every 15 days ± 2 days starting on Day 1. All doses will be scheduled relative to Day 1, not relative to the prior dose. If needed, dose adjustments will occur monthly until dose stabilization is achieved. Once maintenance dose is achieved, further adjustments may be made at the discretion of the Investigator while keeping IGF-I at day 7 post-dose between 0 - 2.0 SDS.

4.4 Method of Assigning Subjects to Treatment Groups and Subject Number Assignments

Enrollment into the study will be based on the order of appearance of subjects completing Screening activities with approval by the Medical Monitor. A unique Subject Number will be sequentially assigned to each subject. Subject numbers will not be re-assigned.

4.5 Concomitant Therapy

Restrictions on prior and concomitant therapy are provided in the Inclusion and Exclusion Criteria (Sections 3.7 and 3.8). At Screening, subjects may have completed a Versartis adult GHD study, be rhGH treatment naïve, or, if currently receiving daily rhGH injections for treatment of GHD, must undergo a minimum of a 14-day wash-out period prior to initiating study treatment (Section 6.2). Any underlying disorders associated with GHD must have been clinically stable for at least six months. For subjects taking other hormone replacement therapy, they must have been on a stable course of treatment for at least three months prior to Screening (routine dose adjustments are considered part of a stable course of treatment). Adjustments to these medications (thyroid, glucocorticoid and antidiuretic hormones) are permitted during the protocol as required by standard medical practice.

If subjects are diagnosed with adrenal insufficiency at Screening, subject must be placed on stable glucocorticoid treatment doses for at least 30 days prior to enrollment. These subjects may re-enter screening after stabilization of glucocorticoid treatment. Other prior or concomitant therapy will be reviewed and approved by the Investigator and the Medical Monitor.

4.6 Restrictions

There are no restrictions on diet or exercise for these subjects.

4.7 Treatment Compliance

Administration of all somavaratan doses will be performed in clinic by a trained health care professional during the dose titration period. Subsequent maintenance doses can be administered by trained subjects/caregivers, or a health care professional. Dosing schedules will be established at the time of enrollment. Each dose has a window of ± 2 days, but monthly variability will not affect overall treatment schedule, because dates of administration are relative to the first dose. If a dose cannot be administered within this time window, it will be considered a missed dose, unless the Investigator and Medical Monitor decide to administer the dose as a protocol deviation (e.g., outside of the protocol-specified dosing window of every 15 days ± 2 days). Failure to receive scheduled doses may be cause for withdrawal.

Efforts should be made to complete all protocol specified activities within the allotted time frame. Failure to adhere to the schedule for PK/PD and safety data sample collection may be cause for withdrawal.

4.8 Packaging and Labeling

4.8.1 Somavaratan

Somavaratan Drug Product (sterile parenteral study medication, DP) will be provided by the Sponsor to Catalent Pharma Solutions (Catalent). Catalent will label the DP and distribute a sufficient quantity of single-unit dose containers of DP with tamper evident seals to the participating investigational pharmacy at each site. The DP will be provided as labeled 2 mL glass vials with a rubber stopper and a crimp seal with flip top lid or as a disposable autoinjector device (when available). Vials are designed to allow for withdrawal of 1.0 mL (100 mg) of DP. Disposable autoinjector devices are for single use only and provide the ability to select (dial) the prescribed mg dose of somavaratan between 20 and 100 mg (4 separate presentations with 20 mg range each).

4.8.2 Assembly and Labeling of Somavaratan

4.8.2.1 Vial and Syringe Configuration

Dispensing of the unit doses into syringes for subject administration for all in clinic dosing events will be the responsibility of the pharmacist or other site healthcare professional in compliance with the site practices and local regulatory requirements.

Dispensing of the unit doses into syringes for subject administration for doses administered outside of the clinic by subject/caregiver will be the responsibility of each subject/caregiver. Dose administration by subject/caregiver will be allowed only after adequate training and documentation of demonstrated understanding by subject/caregiver. Dose administration outside of the clinic will be performed by a health care professional or trained subject/caregiver only.

The DP will be labeled as somavaratan for investigational use only.

4.8.2.2 Somavaratan Autoinjector

Dispensing of the somavaratan autoinjector (when available) to the subject for subject dose administration for all dosing events will be the responsibility of the pharmacist or other site healthcare professional in compliance with the site practices and local regulatory requirements.

Dose administration by subject/caregiver will be allowed only after adequate training and documentation of demonstrated understanding by subject/caregiver. Dose administration outside of the clinic will be performed by a health care professional or trained subject/caregiver only.

The somavaratan autoinjector will be labeled for investigational use only.

4.9 Storage and Accountability

4.9.1 Somavaratan

The DP will be stored at 2–8° C at the investigational pharmacy. DP storage at the investigational pharmacy will have restricted access. The DP will be removed from cold storage and allowed to equilibrate to room temperature for a minimum of 30 minutes before subject administration. No special procedures are required for the safe handling of the DP, however, it must be handled gently (e.g., no shaking, agitating, heating under warm water, etc.). The DP will remain stable for a minimum of 8 hours at ambient temperature. Directions for use and administration will be provided. Documentation of somavaratan doses administered will be entered directly by the person administering the doses (subject/caregiver or health care professional) into the interactive web response system (IWRS) provided by Versartis.

4.10 Investigational Product Retention at Study Site

Records will be maintained showing the receipt and disposition of all DP (vials and/or autoinjectors) and other study supplies (if applicable). The Sponsor and/or its designee will routinely monitor and audit the records of DP receipt, supplies, storage, dosage preparation procedures, and records at the investigational pharmacy. For all used DP vials, the empty used vials will be discarded upon satisfactory completion of accountability procedures. All used autoinjectors will be discarded upon satisfactory completion of accountability procedures. Any unused DP will be retained until completion of the study.

Following completion of the clinical phase of the study and Sponsor review of accountability, all unused, used or partially used DP and study supplies will either be returned to the Sponsor (together with the accountability records) or will be destroyed at the clinical site and Certificates of Destruction (or equivalent) provided to the Sponsor.

DP must be controlled and accounted for by the study Investigator or the designee; however, the study Investigator retains primary responsibility for its use and documentation of use. No persons other than those designated as qualified study participants may receive study medication. The study Investigator or physician sub-Investigators are the only persons authorized to provide medication orders or prescribe study treatments.

The study Investigator must ensure that DP is stored under the specified conditions and in a secure location with access limited to those involved in the study or other appropriate study site personnel. Additionally, the study Investigator must allow access to Versartis, Clinical Research Associates (CRAs), auditors and regulatory authorities for inspection of records and investigational product supplies.

5 STUDY PROCEDURES

For subjects who participated in a previous somavaratan study:

- Up to 30 day Enrollment period for Inclusion/Exclusion Criteria; the Day 1 visit may occur simultaneously with the last visit of the subject's previous somavaratan study
- Subjects receiving somavaratan once monthly in a prior Versartis adult GHD study or in this study, irrespective of the cohort assignment and whether they have achieved maintenance dosing, will transition to receive treatment at half of their current dose (rounded down to the nearest even number, minimum dose of 20 mg).
- Monthly dose titration period (Table 2) with adjustments to somavaratan doses as needed
- Twice-monthly treatment with maintenance dose of somavaratan

For new subjects who are either receiving daily rhGH therapy or are treatment naive:

- Up to 30 day Screening period for Inclusion/Exclusion Criteria
  - Minimum of 14 day washout period for subjects currently receiving daily rhGH treatment
- Fixed starting dose (Table 1) with monthly dose titration period (Table 2) with adjustments to somavaratan doses as needed
- Twice-monthly treatment with maintenance dose of somavaratan

All subjects will have Day 8 IGF-I SDS evaluated each month with subsequent dose adjustments made per the Dose Titration Plan (Table 2)

5.1 Screening procedures

Subjects may undergo study specific Screening/Enrollment activities up to 30 days prior to enrollment in the study. Subjects will sign the study-specific informed consent form in the presence of an Investigator prior to any Screening/Enrollment procedures being performed. Subjects are enrolled in the study after fulfilment of the Inclusion/Exclusion Criteria.

5.2 Medical History

A complete medical history and Baseline signs and symptoms will be obtained as part of enrollment activities during the Screening visit.

5.3 Physical Examination

A physical examination will be performed at Screening and quarterly thereafter (Month 3, 6, 9, 12, etc.). During dose titration, a symptom-directed brief physical examination will also be performed at monthly clinic visits. Injection sites will be examined at all clinic visits.

5.4 Vital Signs

Vital signs and weight are measured at the beginning of all clinic visits. Weight will be measured with subject wearing light clothing and without shoes. Pulse rate, respiration rate, body temperature, and systolic/diastolic blood pressure will be measured at all clinic visits with the subject sitting quietly for at least five minutes.

5.5 Clinical Laboratory Tests

5.5.1 Laboratory Parameters

Subjects will be in a seated or supine position during blood collection. Growth hormone stimulation tests (if necessary for diagnosis of GHD) and adrenal stimulation tests will be performed locally according to institutional protocols. Urine tests will performed locally. All other clinical laboratory tests will be conducted by a central laboratory to be identified by the Sponsor and include the following:

Table 3 List of Laboratory Tests

<table>
<tr>
<td>Hematology:
– Red blood cell (RBC) count
– White blood cell (WBC) with differential
– Platelet count
– Hemoglobin (Hgb)
– Hematocrit (Hct)
– Mean corpuscular hemoglobin (MCH)
– Mean corpuscular hemoglobin concentration (MCHC)
– Mean corpuscular volume (MCV)</td>
<td rowspan="3">Serum Chemistry:
– Albumin (ALB)
– Alkaline phosphatase (ALP)
– Alanine aminotransferase (ALT; SGPT)
– Aspartate aminotransferase (AST; SGOT)
– Blood urea nitrogen (BUN)
– Calcium (Ca)
– Cortisol (am baseline and stimulated)[1]
– Creatinine
– Gamma-glutamyl transpeptidase (GGT)
– Glucose
– Phosphate
– Potassium (K)
– Sodium (Na)
– Total protein
– Free T4
– TSH
– High-sensitivity C-reactive protein (hs-CRP)

1: Adrenal stimulation testing will be performed locally (for subjects without documented history of adrenal insufficiency) at Screening. Additional adrenal testing may be performed at the discretion of the Investigator based on clinical assessment.</td>
</tr>
<tr>
<td>Urinalysis: performed locally by Urine Multistix® (or similar)
– Bilirubin
– Glucose
– Ketones
– Nitrite
– Occult blood
– pH
– Protein
– Urobilinogen</td>
</tr>
<tr>
<td>Pregnancy test: (for women of child bearing potential)
– Serum at Screening
– Urine at all other time points</td>
</tr>
<tr>
<td>Fasting Lipid profile:
– Total cholesterol
– Low density lipoprotein (LDL)
– High density lipoprotein (HDL)
– Triglycerides
– Ratio of total/LDL cholesterol</td>
<td>Glucose metabolism:
– Fasting insulin
– Fasting glucose
– Hemoglobin A1c (HbA1c)</td>
</tr>
</table>

Pharmacokinetics: – Somavaratan plasma concentration	Pharmacodynamics: – IGF-I – IGFBP-3
Immunogenicity: – Anti-drug antibodies (ADA) detection and characterization	

5.5.2 Sample Collection, Storage, and Shipping

The safety, PK/PD and immunogenicity assessments require blood samples to be collected during the study. The total annual blood volume required to be collected over the course of the study will differ depending on the duration of dose titration. Estimated annual maximum blood sample volumes (based on 4 months of titration) are detailed in Table 4 below:

Table 4 Maximum Annual Blood Volumes Required

Sample Type	Blood Volume (mL) per Sample	Collection Schedule[1]							Total Number of Time-points	Total per Subject (mL)
		Screen	D1	M1,2	M3	M6	M9	M12		
Hematology (CBC)	2.0	X	X		X	X	X	X	**6**	12.0
Chemistry, lipid, thyroid panel	10.5	X	X		X	X	X	X	**6**	63.0
Glucose metabolism	9.5	X	X		X	X	X	X	**6**	57.0
PK[2]	2.0		X	X	X	X	X	X	**18**	36.0
PD[2]	7.0	X	X	X	X	X	X	X	**19**	133.0
Immunogenicity	3.5		X	X	X	X	X	X	**6**	21 .0
ACTH stim test	8.0	X							**1**	8
Pregnancy (hCG)	3.5	X							**1**	3.5
Total Maximum Annual Blood Volume Collection										**333.5**

1: After the first year all blood sample collections will occur every 6 months.

2: PK/PD samples (IGF-I and IGFBP-3) are to be collected at pre-dose and 7 days after dosing (Day 8 ± 1 day) of each month until maintenance dosing is achieved and then quarterly thereafter (maximum volume calculations assume 4 months of titration).

5.6 Dispensing Study Drug

5.6.1 During Titration Period

All Day 1 somavaratan doses during titration will be prepared and administered in clinic by a qualified health care professional. Day 16 somavaratan doses may be administered in clinic or at home by trained subjects/caregivers, or a health care professional

5.6.2 During Maintenance Period

All somavaratan doses be administered in clinic or at home by trained subjects/caregivers, or a health care professional.

5.6.3 Dispensation Records

The study Investigator must maintain adequate records of receipt, dispensing and return/destruction of all DP. Shipments of DP will be reviewed upon receipt and contents verified with notification sent to the Sponsor or its designee. Exact records of dispensation and return from investigational pharmacy must be maintained including the following information:

- Identification of study subject by study number and initials
- Date of dispensation
- Quantity of DP vials and/or autoinjector devices dispensed (primary container)
- Signature and date of dispensing pharmacist or other trained/authorized personnel
- Date used/unused DP are returned to site

An Investigational Product Accountability Log will be provided by the Sponsor or its designee. Institution-required logs/documents may be used provided they contain the study-required elements and are approved by the Sponsor or its designee.

All dispensed DP vials and/or autoinjector devices (used, partially used or unused) will be returned to the site for drug accountability reconciliation. Other study supplies used at home may be discarded by the subjects/caregivers. Safety containers will be provided to subjects/caregivers for safe disposal of used needles and syringes and/or return of used autoinjector devices. After verification by the Study Monitor, the unused somavaratan DP and other study supplies used on site may be destroyed or returned to the Sponsor's designated investigational product storage facility. Details for destruction and/or return are provided in the Pharmacy Manual.

5.7 Adverse Event Assessments

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

AEs may include increases in intensity or frequency of conditions or diseases that were pre-existing prior to study participation. Examples might include a subject in whom routine headaches become more severe or begin to occur more frequently. Medical or surgical procedures are not in and of themselves considered AEs, but if a condition or disease led to the

procedure, the condition or disease would be considered an AE unless it was present prior to entering the study and did not worsen after entering the study.

AEs may include sequelae of overdose, drug abuse/misuse reports, lack of efficacy, or occupational exposure. In the absence of associated sequelae, these events should be reported as Special Situations and not AEs. Situations in which an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery or social reasons) are also not considered AEs.

AEs will be reported using the terms in the CTCAE V.4.0 grading scale. A copy will be supplied in the Study Manual, and it can be found online at http://evs.nci.nih.gov/ftp1/CTCAE and http://safetyprofiler-ctep.nci.nih.gov/ctc/ctc.aspx.

Subjects entering the study with ongoing Baseline medical conditions should have their signs/symptoms graded according to CTCAE V.4.0 criteria. Increases in CTCAE V.4.0 grading from Baseline conditions (e.g., Grade 1 to Grade 2) will be considered adverse events.

A non-serious AE is any AE that does not meet the definition of a serious adverse event below.

5.7.1 Performing Adverse Events Assessments

AEs will be collected at each visit to the health care facility.

5.7.2 Timing

Recording of AEs should begin after informed consent is obtained. AEs occurring after study drug administration are treatment emergent AEs.

5.7.3 Severity

AEs will be assessed for severity (intensity) according to the clinical description provided in the CTCAE V.4.0 grading scale (Grade 1, Grade 2, Grade 3, Grade 4, or Grade 5). If an AE cannot be classified using CTCAE V.4.0 terminology, severity will be assessed using the following definitions listed in Table 5.

Table 5 Adverse Event Severity

Grade 1	**Mild**	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	**Moderate**	Minimal, local, or noninvasive intervention indicated; limiting instrumental activities of daily living.[1]
Grade 3	**Severe**	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limited self-care activities of daily living.[2]
Grade 4	**Life-threatening**	Life-threatening consequences; urgent intervention indicated.

Grade 5	**Death**	Death related to the AE.

1: Examples of instrumental activities of daily living are: using computers, phones, watching TV, reading, etc.

2: Examples of self-care activities of daily living are: bathing, dressing and undressing, feeding self, using the toilet, taking medications, etc.

5.7.4 Adverse Event Relationship

For each AE, the Investigator is required to assess the causal relationship (relatedness) between the administration of the study drug and the occurrence of the AE. The Investigator should use his or her clinical judgment and the following definitions to determine relatedness.

- **Unrelated**: Evidence exists that the adverse event has an etiology other than the study drug; and/or the AE has no plausible temporal relationship to administration of the study drug. For SAEs, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).

- **Related:** There is a reasonable possibility that the event may have been caused by the study drug, including a plausible temporal relationship between AE onset and administration of the study drug, and the lack of a clear alternative etiology.

5.7.5 Related Adverse Events Experienced in Somavaratan AGHD Clinical Trials

Adverse events associated with somavaratan administration have been generally mild and transient and have been similar to those typically observed when rhGH is introduced in GHD patients. At this time, there are no specific events which are considered expected with somavaratan. However, adverse events reported as related to somavaratan treatment in GHD adults include:

- Injection site reaction (erythema, edema, pruritus, swelling, warmth, macule)
- Injection site pain
- Headache
- Myalgia
- Arthralgia
- Muscle fatigue
- Rash
- Erythematous rash
- Nausea
- Generalized edema
- Paresthesia
- Generalized pruritus
- Skin warmth
- Increased cholesterol (LDL, triglycerides)
- Increased lymphocytes

5.7.6 Vital Signs, Physical Examination and Clinical Laboratory Adverse Events

Laboratory abnormalities and changes in vital signs or physical examination findings are considered AEs only if they are determined to be clinically significant by the Investigator, result in withdrawal from the study, necessitate therapeutic intervention, or for some other reason the Investigator considers them clinically important. However, if any of these changes in laboratory, vital signs or physical examinations is attributable to a new disease or condition or a worsening of a condition pre-existing at study enrollment, the disease or condition itself shall be the reported AE, not the change in laboratory, vital sign or physical examination.

5.7.7 Serious Adverse Events

5.7.7.1 Definition

A serious adverse event (SAE) is defined by federal regulation as any AE occurring at any dose that results in any of the following outcomes: death, life-threatening AE, hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Medically significant events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

5.7.7.2 Reporting Adverse Events, Pregnancies, and Serious Adverse Events

All AEs and SAEs, regardless of relatedness, that occur after informed consent until the end of the protocol-required post treatment follow-up period, must be reported as instructed. This also includes any events resulting from protocol-associated procedures performed after informed consent is signed.

All pregnancies (subjects and their partners) that occur from initiation of study medication until 4 weeks after last administration of study medication must be reported to the Sponsor’s contracted pharmacovigilance vendor using the Pregnancy Data Collection form provided, as instructed.

All AEs and pregnancies (subjects and their partners) should be followed up until resolution if possible. If the AE has not resolved by the last day on study, the AE will be followed up until the Investigator and/or the Sponsor determines that the subject's condition is stable. However, the Sponsor may request that certain AEs be followed until resolution.

Investigators are not obligated to actively seek SAEs after study participation has concluded. However, if the Investigator learns of any post-study SAEs that are deemed relevant to the use of study medication, he/she should promptly document and report the event to the Sponsor.

All SAEs must be reported to Premier Research within 24 hours of discovery, by faxing the report to one of the following numbers or sending by email:

Attention: Pharmacovigilance

US Fax Number: [redacted]

US email: [redacted]

EU Fax Number: [redacted]

EU email: [redacted]

The written report should be submitted on the SAE form provided for this purpose. The report must include the Investigator's opinion as to whether the event is study drug-related. If the event is determined to be related to study drug, evidence to support this assessment must also be provided.

Complete reconciliation of SAEs often requires follow up and review of medications, terminology, treatments administered, start and stop dates, and subject discharge records. The study Investigator has ultimate responsibility to ensure complete review and follow up of SAEs as required.

5.8 Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable US FDA Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the Sponsor may be required to expedite to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions (SADRs), or suspected unexpected serious adverse reactions (SUSARs). In accordance with the EU Clinical Trials Directive (2001/20/EC), the Sponsor or a specified designee will notify worldwide regulatory agencies and the relevant IEC in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined by the Sponsor using reference safety information specified in the Investigator's brochure or relevant local label as applicable.

All Investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any study IMP. The Investigator should notify the IRB or IEC of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

5.9 Concomitant Medication Assessments

All concomitant medications reported during the study period will be recorded and assessed for all subjects.

5.10 Removal of Subjects from the Trial or Study Drug

The subject may be withdrawn from the study for any of the following reasons:

- A protocol violation occurs
- A serious or intolerable adverse event occurs
- A clinically significant change in a laboratory parameter occurs
- The subject does not adhere to dosing schedules or specified evaluations are not completed
- The Sponsor terminates the study
- The Investigator determines a subject should not continue study treatment
- The subject requests to be discontinued from the study
- A stopping criteria is met

5.11 Appropriateness of Measurements

The PK/PD and safety assessments are standard in clinical trials of growth hormone replacement agents in adults.

6 STUDY ACTIVITIES

Study activities are described in Section 6.1 and Appendix 1.

6.1 All Subjects

6.1.1 Screening

Subjects will sign the study-specific consent in the presence of a study research health care professional familiar with the protocol and the process of providing informed consent. Subjects may undergo study specific Screening activities only after consent is provided and up to 30 days prior to enrollment (Day 1) in the study. For subjects who participated in a previous Versartis study, assessments from the previous somavaratan study may be used for entry into this study (if conducted within the previous 30 days). Subjects are considered enrolled in the study after providing written informed consent and fulfillment of the inclusion/exclusion criteria.

During the Screening period subjects will have the following procedures and activities performed:

1. Informed consent.
2. Verification of inclusion/exclusion criteria.
3. Medical history including documentation of Baseline signs and symptoms (ongoing observations documented using CTCAE V.4.0 grading scale).
4. Full physical exam.
5. Vital signs including respiratory rate, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
6. Body weight measured in light clothing and without shoes.
7. 12-lead ECG (new naïve to somavaratan subjects only, triplicate tracings required).
8. In new naïve to somavaratan subjects only, collection of blood samples for PD.
9. Serum pregnancy test for women of child bearing potential (Appendix 2). Urine test acceptable for subjects who participated in a previous Versartis study.
10. Collection of fasting blood samples for hematology, serum chemistry, lipid profile, glucose metabolism and thyroid function tests.
11. Adrenal stimulation testing (if subject is not on glucocorticoid replacement for adrenal insufficiency or if adrenal function has not been evaluated in the 3 months prior to Screening).
12. Urinalysis by urine Multistix® (or similar).

13. Recording of AEs using the CTCAE V.4.0 grading scale.
14. Recording of all concomitant medications.

6.1.2 Visit Day 1 Procedures

Subjects may undergo study specific Day 1 activities only after consent is provided and subject enrollment is approved by the Medical Monitor and subject number is assigned. For subjects who completed a previous Versartis study, the End of Study assessments from the previous somavaratan study may be used for entry into this study (if conducted within the previous 30 days). Assessments on Visit Day 1 to be obtained prior to dosing include:

1. Brief physical exam (brief, problem-specific exam may be performed for any reported AE at the discretion of the Investigator). Ongoing observations documented using CTCAE V.4.0 scale.
2. Vital signs including respiration, pulse rate and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
3. Body weight measured in light clothing and without shoes.
4. Collection of pre-dose blood samples for PD (IGF-I and IGFBP-3) PK and immunogenicity
5. Urine pregnancy test.
6. Recording of AEs using the CTCAE V.4.0 grading scale.
7. Recording of all concomitant medications.
8. Somavaratan dose administered in clinic by a qualified health care professional.
9. Scheduling of next site visit.
10. Training on process for study drug storage, preparation, administration and how to document dosing information into the IWRS system.

6.1.3 First Month Procedures

All subjects will begin twice-monthly somavaratan treatment during the first month with in clinic study drug administration required on Day 1 and Day 16. Twice-monthly somavaratan dosing should occur every 15 days ± 2 days. Blood samples will be obtained on Day 8, 16, and 23 for PK and PD assessment. Blood samples on Days 1 and 16 are intended as trough samples and should be collected pre-dose. Blood samples on Day 8 and 23 are intended as peak samples and may be collected at the subject's home by an at-home health care provider. All blood sample collections should occur within ± 1 day of the target collection day, with trough samples always collected pre-dose. In new naïve to somavaratan treatment subjects only, 12-lead ECGs shall be collected 3 days (± 1 day) after Day 1 dosing during the first Month (triplicate tracings).

Recording of concomitant medications, adverse events and study drug administration will be performed for all subjects.

6.1.4 Monthly Visits During Titration

During monthly dose titration in clinic study drug administration will be required on Day 1 of each month. Twice-monthly somavaratan dosing should occur every 15 days ± 2 days. At home dosing is permitted for the Day 16 injection. Blood samples will be collected on Days 1 and 8 for PK and PD assessment. Blood samples on Day 1 are intended as trough samples and should be collected pre-dose. Blood samples on Day 8 are intended as peak samples. Blood sample collection on Day 8 may be conducted at the subjects' home by an at-home health care provider. All blood sample collections should occur within ± 1 day of the target collection day, with trough samples always collected pre-dose. Subjects will return to the site at the end of each month during titration for an assessment and collection of blood samples and somavaratan dosing. Assessments to be obtained on Day 1 of each month during titration and prior to dosing include:

1. Brief physical exam (brief, problem-specific exam may be performed for any reported AE at the discretion of the Investigator). Injection sites will be inspected at all visits.
2. Vital signs including respiratory rate, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
3. Body weight measured in light clothing and without shoes.
4. In new naïve to somavaratan treatment subjects only, 12-lead ECGs shall be collected 3 days (± 1 day) after the Month 4 Day 1 dosing.
5. In new naïve to somavaratan treatment subjects only, collection of pre-dose blood samples for immunogenicity (ADA) at the Month 1 visit (approximately 30 days after Day 1).
6. Recording of AEs using the CTCAE V.4.0 grading scale.
7. Recording of all concomitant medications.
8. Somavaratan dose administered in clinic by a qualified health care professional.
9. Scheduling of next site visit.
10. Dispense study drug for subsequent doses until next clinic visit.

6.1.5 Quarterly Visits: Visit Month 3, 6, 9 and 12 Procedures

Subjects will return to the site at the end of Months 3, 6, 9 and 12 (± 3 days) for an assessment and collection of blood samples. Assessments on Visit Months 3, 6, 9 and 12 include:

1. Physical exam.

2. Vital signs including respiratory rate, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
3. Body weight measured in light clothing and without shoes.
4. Collection of pre-dose blood samples for PK and PD (IGF-I, IGFBP-3).
5. Additional PK and PD samples will be drawn 7 days after dosing (Day 8 ± 1 day).
6. Collection of pre-dose blood samples for immunogenicity (ADA).
7. Collection of fasting blood samples for hematology, serum chemistry, lipid profile, glucose metabolism and thyroid function tests.
8. Urinalysis by urine Multistix® (or similar).
9. Urine pregnancy test for women of child bearing potential (Appendix 2).
10. Recording of AEs using the CTCAE V.4.0 grading scale.
11. Recording of all concomitant medications.
12. Somavaratan dose may be administered in clinic by a qualified health care professional.
13. Dispense study drug for subsequent doses.
14. Scheduling of next site visit (for the subsequent quarter if the subject is on maintenance dose or the subsequent month if further dose adjustment is necessary).

6.1.6 Subsequent Years of Quarterly Visits

After completion of the first year of treatment, subjects will return to the site for quarterly visits (Months 15, 18, 21, etc. (± 3 days) for an assessment and collection of blood samples. Assessments at these visits include:

1. Physical exam.
2. Vital signs including respiratory rate, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
3. Body weight measured in light clothing and without shoes.
4. Blood samples collected every 6 months (e.g., Month 18, Month 24, Month 30, etc.) for:
    a. Pre-dose blood samples for PK and PD (IGF-I, IGFBP-3).
    b. PK and PD samples will be drawn 7 days after dosing (Day 8 ± 1 day).
    c. Pre-dose blood samples for immunogenicity (ADA).
    d. Fasting blood samples for hematology, serum chemistry, lipid profile, glucose metabolism and thyroid function tests.
5. Urinalysis by urine Multistix® (or similar).

6. Urine pregnancy test for women of child bearing potential (Appendix 3).
7. Recording of AEs using the CTCAE V.4.0 grading scale.
8. Recording of all concomitant medications.
9. Somavaratan dose may be administered in clinic by a qualified health care professional.
10. Scheduling of next site visit.
11. Dispense study drug for subsequent months.

6.1.7 Termination Visit

For subjects who terminate their participation in this study, the following assessments should be performed (not required for any assessments performed within the prior 14 days):

1. Physical exam.
2. Vital signs including respiratory rate, pulse rate, and systolic/diastolic blood pressure taken after 5 minutes' rest in a sitting position.
3. Body weight measured in light clothing and without shoes.
4. Collection of blood samples for PK (somavaratan plasma concentration) and PD (IGF-I, IGFBP-3).
5. Collection of blood samples for immunogenicity.
6. Collection of fasting blood samples for hematology, serum chemistry, lipid profile, glucose metabolism and thyroid function tests.
7. Urinalysis by urine Multistix® (or similar).
8. Urine pregnancy test for women of child bearing potential
9. Recording of AEs using the CTCAE V.4.0 grading scale.
10. Recording of all concomitant medications.

6.1.8 Follow Up Procedures

For subjects who terminate the study at any time, follow up should be conducted 60 days (± 3 days) after their final study dose. This may be conducted in clinic or by telephone contact and will include the collection of adverse events and concomitant medications. Subjects with an ongoing AE will be followed-up until the AE is resolved or stable. Subjects may be requested to return to the clinic approximately 3 months after study discontinuation for safety evaluation and blood sample collection.

7 QUALITY CONTROL AND ASSURANCE

This study will be conducted in accordance with the Food and Drug Association (FDA) Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) consolidated guideline (April 2011). These guidelines include:

21 Code of Federal Regulations (CFR) parts 11, 50, 54, 56, 312 and 314

ICH E2a & ICH E6 (R1)

7.1 Adherence to the Protocol

The Principal Investigator and all personnel involved with the conduct of the study agree to adopt all reasonable measures to record data in accordance with the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the Investigator(s). All such deviations will be documented in the study records, together with the reason for their occurrence; where appropriate, deviations will be detailed in the clinical study report and provided in a timely manner to the Sponsor, Sponsor's designee and research site Institutional Review Board (IRB) or Independent Ethics Committee (IEC) per IRB/IEC guidelines.

Quality assurance audits of Investigator sites, CRO, and Sponsor study practices/procedures may occur. Any findings from quality assurance audits related to the study will be reported to the Medical Monitor and Study Director.

8 PLANNED STATISTICAL METHODS

8.1 General Considerations

This section presents a brief summary of the planned statistical analyses. A statistical analysis plan that describes the details of the analyses to be conducted will be finalized prior to database lock and un-blinding.

All summaries will be presented by cohort.

Summary statistics will be provided for the variables described below as follows. For continuous variables, these statistics will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, these statistics will include the number and percentage of subjects in each category.

The last observation obtained prior to the first dose in the current study will be used as the Baseline value for calculating change from Baseline.

8.2 Analysis Populations

8.2.1 Safety Population

The safety population will consist of all subjects who receive any amount of study drug.

8.3 Demographics and Baseline Characteristics

Demographic and Baseline characteristics (including age, gender, race, weight, height, BMI, Baseline IGF-I level and IGF-I SDS) will be summarized by cohort and for the overall population using descriptive statistics.

Medical history and clinical laboratory tests results will be listed.

Prior and concomitant medications will be summarized by cohort and by the number and percentage of subjects taking each medication.

8.4 Objectives

The primary objective of this study is:

- To evaluate the safety of somavaratan during long-term treatment in adults with GHD

The secondary objectives of this study are:

- To evaluate the dose (starting and maintenance) and the dose titration plan of twice-monthly somavaratan during long-term treatment
- To evaluate the immunogenicity of somavaratan during long-term treatment in adults with GHD by detection and characterization of anti-somavaratan antibodies (anti-drug antibodies, ADAs)

- To evaluate pharmacodynamic responses (IGF-I, IGFBP-3) during long-term somavaratan treatment

Somavaratan ADAs will be summarized descriptively.

8.5 Safety

Safety analyses will be conducted on the safety population and will be summarized by cohort. Safety variables include AEs, clinical laboratory values, vital signs, and physical examination results.

AEs will be coded using MedDRA and will be summarized using the coded terms. Summaries of all treatment emergent adverse events (TEAEs), serious adverse events (SAEs) and Suspected, Unexpected Serious Adverse Reactions (SUSARs) will be presented. The incidence of CTCAE V.4.0 Grade 3 or 4 adverse events will be classified according to severity and relationship to study drug.

Observed and change from Baseline values for laboratory safety panels and vital signs will be summarized using descriptive statistics. Laboratory results will also be summarized and presented as shifts from Baseline.

No formal inferential analyses will be conducted for safety variables.

8.6 Retention of Data

All primary data generated in the study and described by Premier, a Contract Research Organization (CRO) (or copies thereof [e.g., laboratory records, data sheets, correspondence, photographs and computer records]), which are a result of the original observations and activities of the clinical study, and are necessary for the reconstruction and evaluation of the study report, will be retained in the Premier archive for a period of 5 years after issue of the final report. At this time, the Sponsor will be contacted to determine whether the data should be returned, retained or destroyed on their behalf. No data will be destroyed without the agreement of the Sponsor.

All study-related records must be retained until 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. The Sponsor will inform the Investigator/Institution when the documents no longer need to be retained. The Investigator must obtain approval in writing from the Sponsor prior to destruction of any records. Typically, these records will be held in the Investigator's archives. If the Investigator is unable to meet this obligation, the Investigator must obtain permission from the Sponsor to make alternative arrangements. Details of these arrangements must be documented in writing to the Sponsor.

Specimens requiring frozen storage are specifically excluded from the above. These will be retained for as long as the quality of the material permits evaluation but for no longer than 6 months after completion of the study (defined as issuance of Clinical Study Report). The Sponsor will be notified of the intent to destroy samples and any financial implications before specimens are destroyed on their behalf.

8.7 Interim Analysis

No formal Interim analysis is planned however data from this study may be analyzed periodically to assess the dosing regimen and allow adjustments to alleviate safety concerns or optimize normalization of IGF-I SDS responses.

9 ADMINISTRATIVE CONSIDERATIONS

9.1 Investigators and Study Administrative Structure

The Sponsor has an agreement with Premier Research (Premier), a CRO, to provide project management oversight for this protocol. Premier has been assigned many study oversight responsibilities for the protocol conduct. A formal transfer of obligations document outlines the activities assigned to Premier.

9.2 Institutional Review Board (IRB) or Independent Ethics Committee (IEC) Approval

The Investigator will initiate and enroll subjects only after IRB/IEC approval of the protocol and the informed consent documents have been received. All recruiting materials used in the study must have IRB/IEC approval. Progress reports regarding the study will be submitted to the IRB/IEC in accordance with institutional and regulatory guidelines.

9.3 Ethical Conduct of the Study

The study will be performed in compliance with the FDA CFR for GCP and ICH Regulations. These procedures ensure the protection of the rights and the integrity of the subjects, adequate and correct conduct of all study procedures, adequate data collection, adequate documentation and adequate data verification. The Standard Operating Procedures (SOPs) relevant in the context of the study are available at Premier.

9.4 Subject Information and Consent

Before being enrolled, subjects must provide informed consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them. The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained. A copy of the consent document must be given to the subject. The original signed consent document will be retained by the Investigator.

9.5 Subject Confidentiality

Subject confidentiality will be maintained throughout the study according to applicable guidelines, regulations and IRB requirements. All samples, study clinical data, and reports of results will de-identify individual subjects. Subjects will be identified by initials (where allowed), date of birth, gender and subject number only for use in data collection. Published data will provide subject numbers only if needed for clarity of presentation (e.g., in individual event listings).

9.6 Study Monitoring

All investigational sites will receive on site visits from the Sponsor and/or Sponsor designee, Premiere. Site visits may be conducted with representatives from both the Sponsor and Premier in attendance. All sites will receive at a minimum a pre-study qualification visit and a site initiation visit. All sites that enroll subjects into the study will receive routine monitoring visits where source data verification will be conducted by the monitor.

All activated sites will receive study close-out visits by the Study Monitor upon closure of the study.

Premier will develop a monitoring plan that will be approved by the Sponsor and followed for the duration of the study. All study sites must allow direct access to all pertinent study documentation and medical records for enrolled subjects.

9.7 Case Report Forms and Study Records

Source documents must be maintained for each subject during the course of the study. The documents must demonstrate in writing that informed consent was obtained prior to subject participation. Source documents include the signed original informed consent forms (ICFs), medical records including physician notes, nursing flow sheets, and hospital charts. They include documentation of all procedures conducted for the study and are the primary original source for all study data except where otherwise specified.

Electronic Case Report Forms (eCRFs) will be used in this study and must be completed for each enrolled subject.

All protocol-required information collected during the study must be entered by the Investigator or the designee in the eCRF. eCRF completion and correction will be performed in accordance with the study eCRF guidelines.

The Investigator or designee should complete the eCRF pages as soon as possible after the study information is obtained. An explanation should be given for all missing data.

The completed eCRF must be reviewed and signed by the Principal Investigator.

9.8 Protocol Violations/Deviations

Protocol-specified events, visits, tests, and procedures should be followed without exception. In situations where protocol deviations (e.g., missed visits or tests) occur due to unforeseen circumstances, documentation of the reason should be made in the source document and documented by the CRA for inclusion in the Clinical Study Report (CSR).

9.9 Access to Source Documentation

All study data entered into the electronic CRF must be verifiable to the source data. The Sponsor and its delegated representative study monitors and auditors must have access to all original recordings, laboratory reports and enrolled subject's medical records.

9.10 Data Generation and Analysis

Premier (the CRO) will perform the data analysis. The results of the study will be reported together in one clinical study report. A detailed Statistical Analysis Plan describing the methodology to be used will be finalized prior to study enrollment and may be modified as needed and documented prior to database lock.

Premier and the Sponsor will prepare an integrated clinical, pharmacodynamic and pharmacokinetic report. Prior to issuing the final CSR, Premier will prepare a draft report for approval by the Sponsor. The report will be in accordance with the ICH note for Guidance on Structure and Content of CSRs. The draft report may be submitted for Quality Assurance audit, the findings of which will be incorporated into the final version.

9.11 Financial Disclosure

A completed financial disclosure document is required for all Investigators participating in this study.

9.12 Publication and Disclosure Policy

The Sponsor holds all publication rights to the aggregate data obtained from this study. Study Investigators will submit any planned publication of individual site data to Sponsor for review and approval at least 60 days prior to submission to the publisher.

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Appendix 1 Schedule of Events

Activity / Assessment	Screen[1]	Treatment Titration Period			Maintenance Dosing	Additional Visits	Termination[21]
		Day 1	First Month	Monthly Visits	Quarterly Visits		
Informed Consent[2]	X					Continue Quarterly Visit Schedule in Each Subsequent Year	
Inclusion/Exclusion Criteria	X						
Medical History	X						
Baseline Signs and Symptoms	X						
Physical Exam	X				X		X
Brief Physical Exam[3]		X		X			
12-Lead ECG[4]	X		X	X			
Vital Signs[5]	X	X		X	X		X
Body Weight[6]	X	X		X	X		X
Pregnancy test[7]	X[8]	X[9]			X[9]		X[9]
PK Samples[10]		X	X[10]	X[10]	X[10]		X
PD Samples[11]	X[11]	X	X[11]	X[11]	X[11]		X
Immunogenicity[12]		X			X		X
Hematology[13]	X	X			X		X
Chemistry[14]	X	X			X		X
Lipid Profile[15]	X	X			X		X
Glucose Metabolism[16]	X	X			X		X
Thyroid function test[17]	X	X			X		X
ACTH stimulation test[18]	X						
Urinalysis[19]	X	X		X	X		X
Adverse Events	X	X	X	X	X		X
Concomitant Medications	X	X	X	X	X		X
Somavaratan Dosing[20]		X	X	X	X		

1. Screening activities can only occur after consent is provided and may take place up to 30 days prior to dosing (Day 1). For subjects who participated in a previous Versartis study, assessments from the previous somavaratan study may be used for entry into this study (if conducted within the previous 30 days).
2. Informed consent to be completed prior to performing any study related procedures.
3. A directed physical exam to address health complaints and to examine injection sites.
4. For new naïve to somavaratan subjects only, 12-lead ECGs (triplicate tracings) will be conducted at Screening and repeated at Day 1 and Month 4 at 3 days (±1 day) after dosing (in-clinic visit required).
5. Includes temperature, respiratory rate, pulse rate and systolic/diastolic blood pressure taken after 5 minutes rest in a sitting position.
6. Weight to be taken in light clothing and without shoes.
7. For women of child bearing potential (Appendix 2).
8. Serum pregnancy test (urine test acceptable for subjects who participated in a previous somavaratan study).
9. Urine pregnancy test.
10. PK sample is somavaratan plasma concentration, collected on Day 1, 8, 16, and 23 in the first month, on Day 1 and 8 during monthly titration, and on Day 1 and 8 at all quarterly visits during the first year and every 6 months thereafter.
11. PD samples include IGF-I and IGFBP-3, collected on Day 1, 8, 16, and 23 in the first month, on Day 1 and 8 during monthly titration, and on Day 1 and 8 at all quarterly visits during the first year and every 6 months thereafter. In new naïve to somavaratan subjects only, a PD sample is required at Screening.
12. Serum samples will be collected for anti-somavaratan antibodies (ADAs). Samples are to be collected at Screening and pre dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.). New subjects naïve to somavaratan treatment require and additional ADA sample collected pre-dose at M1.
13. Complete blood count and differential. Samples are to be collected at Screening and pre-dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.).
14. Includes ALT, AST, GGT, phosphate, alkaline phosphatase, bilirubin, glucose, calcium, albumin, total protein, potassium, sodium, BUN and creatinine. Samples are to be collected at Screening and pre-dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.).
15. Includes fasting cholesterol, HDL, LDL, triglycerides, ratio of total/LDL cholesterol and hs-CRP. Samples are to be collected at Screening and pre-dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.).
16. Includes fasting insulin and glucose, HbA1c. Samples are to be collected at Screening and pre-dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.).
17. Includes Free T4, TSH. Samples are to be collected at Screening and pre-dose at each quarterly visit (Day 1, M3, M6, M9, and M12) during the first year and every 6 months in subsequent years (e.g., M18, M24, M30, etc.).
18. ACTH stimulation test to be performed locally (within 3 months of screening visit) according to institutional protocol (not required for subjects with a documented history of adrenal insufficiency and who are taking glucocorticoid replacement therapy). Additional ACTH stimulation testing/adrenal function tests may be performed at the discretion of the Investigator per routine clinical practice.
19. Random sample tested by urine Multistix® (or similar), performed locally.
20. Somavaratan dosing commences at Day 1 with all subjects receiving twice-monthly dosing (every 15 days ± 2 days) administered in a vial and syringe configuration or with the somavaratan autoinjector (when available) subcutaneously, at room temperature, in the upper arm, abdomen, buttock or thigh.
21. Perform these assessments for subjects who terminate their participation in this study (not required for any assessments performed within the prior 14 days). For subjects who terminate the study at any time, follow up should be conducted approximately 60 days after their final study dose. This may be conducted in clinic or by telephone contact and will include the collection of adverse events and concomitant medications.

Appendix 2 Definition of Childbearing Potential and Contraceptive Requirements

The risks of treatment with somavaratan during pregnancy have not been evaluated. Please refer to the latest version of the Investigator's Brochure for additional information.

1) Definition of Female of Childbearing Potential

Women < 54 years of age with amenorrhea of any duration will be considered to be of childbearing potential unless they have had a hysterectomy, bilateral oophorectomy, or medically documented ovarian failure.

Women ≥ 54 years of age with cessation of menses for ≥12 months will not be considered to be of childbearing potential.

2) Contraceptive Requirements for Females

Female subjects of childbearing potential must agree to use a highly effective method of contraception from the enrollment visit through 30 days after the last dose of somavaratan. The Investigator should counsel subjects on appropriate methods for avoiding pregnancy during the study. These methods are recommended due to a low failure rate (<1% per year), and include the following:

> Single methods: Copper or LNg Intrauterine Device (IUD), progesterone implant or injection, tubal sterilization*, or vasectomy with documented azospermia 3 months post-procedure
>
> Combination methods: oral contraceptives plus barrier, transdermal patch plus barrier, vaginal ring plus barrier, diaphragm with spermicide plus condom

Abstinence is only considered an acceptable method of contraception if it is a pre-existing part of a subject's lifestyle. Symptom-thermal methods (basal body temperature, cervical mucous, or calendar/rhythm) or withdrawal are not considered adequate forms of contraception for the purposes of this study.

*Tubal sterilization via the Essure procedure is not considered a reliable form of contraception unless tubal blockage is verified by hysterosalpingogram (HSP) approximately 3 months after microinsertion. Prior to verification, another contraception method described above should be used.

3) Contraceptive Requirements for Male Subjects (and their female partners)

All male study participants must agree to consistently and correctly use a condom from Baseline until 90 days after administration of the last dose of study drug. If their female partner is of childbearing potential (as defined above), their female partner must use 1 of the methods of birth control listed above from the date of Screening until 90 days after administration of the last dose of study drug.

Male subjects must agree to refrain from sperm donation for at least 90 days after the last dose of study drug.

4) Procedures to be Followed in the Event of Pregnancy

Subjects will be instructed to notify the Investigator if they or their partner become pregnant at any time during the study, or if they become pregnant within 30 days (90 days for partners of male subjects) of the last somavaratan dose. Subjects who become pregnant or who suspect that they are pregnant must report the information to the Investigator. Subjects whose partner has become pregnant or suspects she is pregnant must report the information to the Investigator. All pregnancies (subjects and their partners) should be followed up until resolution if possible.

Instructions for reporting pregnancy, partner pregnancy, and pregnancy outcome are outlined in Section 5.7.7.2.

Appendix 3 Approval and Signature Page: Principal Investigator

I have read Protocol 15VR8 and agree to conduct the study as outlined. In addition, I agree to conduct the study in compliance with Good Clinical Practice (GCP) and the International Conference on Harmonisation (ICH) Regulations and all guidelines as stated in the protocol and other information supplied to me.

Principal Investigator: Print Name:

Signature: _____

Date: _____